RECONCILIATION OF THE DANISH AND REGENERON FH REPORTS

Central Issue: Published scientific reports are regarded by the industry and regulators as authoritative. The publication strategy has influenced how Familial Hypercholesterolemia (FH) is defined and counted, and thus how patients are selected for risky

The core of this analysis was first put together in November 2016. It focused on the Danish reports. I sent several copies to various federal regulators. In 2017, I brought in the Regeneron report and again sent out copies.

MISINFORMATION IS AN AGENT FOR DISEASE
As far as money can bully the door to the laboratory it will be academic corruption and not contagion itself that spreads ill-health on a vast scale.

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Website: FHprevalence.com
Website: 3footcrowbar.com
Twitter: @3footcrowbar
“Higher Prevalence” is the key to Marketing Drugs

“Higher than Expected Prevalence” is a marketing tool: Dr. Adriane Fugh-Berman, who was expert witness in the Wyeth trial, helped expose widespread abuse in medical literature. She was quoted in a magazine article titled, “Ghostwriters in the medical literature.”

“People tend to think of marketing messages as ‘buy drug A,’ but that’s never the message imbedded in such articles. …. The message may be, disease A is underdiagnosed or far more serious than previously believed ....”¹

Being able to claim “higher prevalence than previously thought” is the ability to claim underdiagnosis. Underdiagnosis leads to the conclusion of undertreatment and undertreatment means that doctors aren’t working hard enough. Higher Prevalence is the cornerstone and once it is set, the rest of the argument falls into place.

Pharma’s² “methodology” achieves this end and that methodology is …

- **The linguistic conflation of distinct diseases into one name:** “FH.”
- **Selecting geographical regions known to have higher than average prevalence.**
- **Lowering standards to harvest errors.**
- **Mathematical shenanigans.**
- **Swapping unprofitable patients out and profitable false positives in.**


Outline through Analogies:

What follows is not a scientific problem: If I said that two pills plus two pills does not equal five pills, I am not talking about pharmacology or medicine. Likewise, my analysis does not lean on the study of science or disease. It leans on math and deduction. As an introduction, here are some analogies of what will follow.

Zebras: If zebras were suddenly called “horses,” would we have more of either or both in the world? These industry-funded efforts are more aptly called linguistic strategies than prevalence studies. A higher than expected prevalence is necessary to sound the alarm of “underdiagnosis.” It is the point of leverage in the publication strategy. And it is a false claim. Separate diseases have been conflated ... a simple linguistic manipulation. In fact, after careful inspection, prevalence for FH-as-LDLR in these reports is actually lower than the established numbers. It’s as if professor A did a prevalence study of domesticated horses, and professor B did the same, but included zebras as if “horses.” If professor B does not explain the conflation of “zebras” with “horses” and claims a higher prevalence of “horses,” he uses culturally inherited assumptions to deceive his readers. See slide on page 6; full analysis on page 14.

Geno-mandering: In the USA, Regeneron continues the geography-management shown in the Danish studies, cherry-picking areas with inordinately high prevalence. Just as politicians can misrepresent the public’s choice through gerrymandering, so can Pharma misrepresent FH prevalence by selecting precisely those regions with higher than average disease prevalence. See Slide on page 7; full analysis on page 24.

A Tomato is not an Apple: Stepping backwards to view a tomato from 20 yards does not make it a red apple. Likewise, lowering standards for diagnosis does not increase a patient population. It inflates the count with false positives. Slide on page 8; full analysis on page 29.

The whole Pie: If someone hands me ¼ of an apple pie, I can subtract ¼ from 1 and calculate the existence of the remaining 3 slices, being ¾ of the pie. If after explaining the procedure, someone hands me a whole strawberry pie, and using the whole strawberry pie as if a fraction of that Apple pie, can I really come up with a “remainder” equal to 3 whole strawberry pies? See slide on page 9; full analysis on page 38.

Galapagos: It’s as if a Galapagos scientist made a special drug and then went out to convince everyone that there is a disease specific to sea-swimming turtles, while showing everyone how easy it is to find and inoculate the land-based tortoises. See slide on page 10; full analysis on page 56.
Detailed Outline of Prevalence Strategy and Tricks

Slide on page 6. Full analysis on page 14. The real “methodology” behind the higher prevalence claim is a linguistic conflation of distinct diseases into the single term, “FH.”

- Before Big Pharma’s publication strategy, those with APOB mutations were defined as FDB. Those with PCSK9 were FH3. Those with LDLR were FH.
- Regeneron’s “new” increase in prevalence requires a linguistic re-definition -- a conflation of FDB and FH3 with “FH.” No screening in the field is required to increase prevalence. No new people are found.
- Using linguistic conflation on established prevalence rates for the separate diseases, mathematics alone arrives at a higher prevalence. This means that the conflated prevalence claimed in the Regeneron-funded report is not higher than previously thought, but actually lower.

Slide on page 7. Full analysis on page 24. Geno-mandering: Big Pharma takes a page from political gerrymandering. This is not science, but information strategy.

- The previous Big Pharma authoritative reports focused on Denmark and The Netherlands. The choice was not accidental.
  1. **White Europeans**: Along with other nations with Central and Northern European ancestry, Denmark has an unusually high APOB mutation prevalence. APOB is relatively rare elsewhere in the world.
  2. **Founder Effect** is a genetic anomaly which results in a higher than usual prevalence of genetic mutations. The influence of founder effect on Danish FH is “intermediate.” U.S. FH is not represented by the Danish.
  3. **Founder Effect**: Another study with financial ties focused on The Netherlands, already documented to be influenced by founder effect.

- Now the Regeneron study moves us from white Europeans to white US residents of European descent.
  1. **White Europeans**: The Regeneron-funded study was of 98.4% whites, who were said to be of European descent.
  2. **Founder Effect**: The study included Lancaster, PA, which includes the Amish. Experts know that their founder effect results in the highest APOB prevalence in the world.

Slide on page 8. Full analysis on page 29. The reports add in groups that inflate results.

- The 1st Danish report lowered the standard of clinical diagnosis without compensating for false positives. It also used “6” on-text as the clinical cutoff point, while using 5 off-text in the actual calculation, inflating the results even further.
- The new Regeneron report discloses that it included a group which was inflated due to selection bias. It did not disclose however the LDLR and APOB breakdown of this inflated group or the breakdown in the population that did not include this group (the less selected population). Most likely a disclosure of this breakdown would emphasize the preponderance of APOB over LDLR in the less selected group, which would put a brighter light on the already present reversal of the established predominance of LDLR prevalence over APOB. Most likely the breakdown would reveal a much lower number of LDLR in the unselected group, lowering prevalence for FH-as-LDLR even further.
Slide on page 9. **Full analysis on page 38. Mathematical Leverage:** Denominators of key fractions were inflated before calculating the results for LDLR (FH) and APOB (FDB) prevalence. For example, in the upper row of the table below, see the calculation of APOB prevalence, which was supposed to be distinct from LDLR -- yet it was calculated with LDLR in the denominator (probands found/total probands: 19/142 = .1338). In the next row down, see APOB without LDLR added in.

<table>
<thead>
<tr>
<th>Isolated ADH constituent</th>
<th>Probands Found</th>
<th>Total Probands</th>
<th>Consequent Fraction of Spectrum Found</th>
<th>Derived total</th>
<th>Prevalence wf Pop. of 98000 Prevalence wf Pop. of 98098</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB with LDLR added</td>
<td>19</td>
<td>142</td>
<td>0.133803</td>
<td>111</td>
<td>118</td>
</tr>
<tr>
<td>(2nd report)</td>
<td></td>
<td></td>
<td></td>
<td>830</td>
<td></td>
</tr>
<tr>
<td>APOB without LDLR</td>
<td>19</td>
<td>19</td>
<td>1</td>
<td>111</td>
<td>118</td>
</tr>
</tbody>
</table>

The inflation of the denominator is also used in the calculation of LDLR prevalence.

**Slide on page 10. Full analysis on page 56.** The move from a genetic-based message to clinical scoring systems in practice swaps patient populations. In 3 steps, these academic molecular reports (1) provoke a sense of urgency with the genetic-based “underdiagnosis,” (2) mildly offer disclaimers of clinical “limitations,” (3) while presenting clinical scoring systems as standard practice. It works because most who pass clinical criteria are not carriers, and on the other hand, most who are genuine carriers do not pass clinical criteria. “Genetic testing [...] is uncommon,” and so ironically, the prevailing clinical diagnostic procedure, regarded as sufficient, contributes to the underdiagnosis. The academic use of genetic testing is only a message of urgency which passes the baton to the realm of action: the applied clinical scoring system, a selection bias in vivo. As this baton changes hands, the genuine mutation carriers are swapped out and the false positives, swapped in.

**Pages 62 & 69: Reconciling the two Danish reports: Deduction exposes a shell game with 2 different constituents:**

See analysis on page 98: “Citation Kiting.” There was no external, contemporary source in the industry’s authoritative report for the new prevalence and the criteria used. This “citation kiting” enables a “conclusion drift.” 1:137 prevalence becomes 1:200 from one report to the other, without a detailed contemporary explanation. A study of FDB-rich “whites of Danish descent” becomes a study of the “general population.” And “FH” as LDLR and “FDB” as APOB become “FH” as both LDLR and APOB.
The recent Pharma-funded effort is more aptly called a linguistic strategy than a prevalence study. “Higher than expected” prevalence is necessary to increase the alarm of “underdiagnosis.” It is the key point within the publication strategy. And it is a false claim.

Established prevalence

- Before Big Pharma’s publication strategy, those with APOB mutations were defined as FDB. Those with PCSK9 were FH.
- Regeneron’s “new” increase in prevalence requires a cultural, linguistic re-definition -- a confession of FDB/FHS with “FH,” not screening in the field. No new quantities are found.
- The linguistic conflation of established rates for the separate diseases, by math alone, arrives at an even higher prevalence. This means that the prevalence claimed in the Regeneron-funded report is not higher than previously thought, but actually lower.

Deception

- The Regeneron-funded study also added in a controversial APOB mutation, a very mild form in vivo which had been excluded as FDB: p.Arg3558Cys. [aka, R353JC,FH353JCys]

In contrast, the Arg3531Cys mutation, which is just as common, is not in itself associated with hypercholesterolemia or an increased risk of ischemic heart disease. — Tybäerg-Hansen, et al.

The real “methodology” is linguistic conflation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defective gene</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>LDLR</td>
<td>1,000,000 / 500 = 2,000</td>
</tr>
<tr>
<td>FDB</td>
<td>LDLR</td>
<td>1,000,000 / 1,000 = 1,000</td>
</tr>
<tr>
<td>FH</td>
<td>FDB</td>
<td>1,000,000 / 2,500 = 400</td>
</tr>
<tr>
<td>p.Arg3558Cys (FH353JCys)</td>
<td>FDB</td>
<td>1,000,000 / 1,103 = 907 (Regeneron-funded study)</td>
</tr>
<tr>
<td>After linguistic conflation of the several diseases into “FH”: Prevalence: 1,000,000 / 4,907 = 1.228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population characteristics</td>
<td>FH variant positive/total</td>
<td>Estimated prevalence</td>
</tr>
<tr>
<td>FH353JCys</td>
<td>172/43,579</td>
<td>1.256</td>
</tr>
<tr>
<td>FDB variant</td>
<td>57/1,052</td>
<td>1.198</td>
</tr>
<tr>
<td>EHR participants</td>
<td>50,726/98</td>
<td>518</td>
</tr>
</tbody>
</table>
| Regeneron’s “increase” in prevalence is all linguistics.

“R3531C mutation in the apolipoprotein B gene is not sufficient to cause hypercholesterolemia.” Rabas JP.
Geno-mandering: Epidemiologists have taken a page from political Gerrymandering

- **Gerrymandering** is where politicians have the power to draw the borders around precisely those voting districts which maximize the outcome of a future election in their own favor.

- **Geno-mandering** is where researchers have the power to draw the borders around precisely those geographic regions which maximize prevalence of a genotype in the favor of Big Pharma.
Both the 1st Danish report and Regeneron’s recent report inserted inflated groups.

The prevalence of individuals classified with definite FH (DLCN criteria > 8 points) was 0.20% (one in 504), probable FH (3–8 points) was 0.53% (one in 189), definite or probable FH combined (>5 points) 0.73% (one in 135), possible FH 6.3% (one in 16) (3–5 points), and unlikely FH 93% (<3 points) (Table 1). The prevalence of

<table>
<thead>
<tr>
<th>FH Type</th>
<th>Total #</th>
<th>Definite FH</th>
<th>Probable FH</th>
<th>Possible FH</th>
<th>Not FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH given to individual</td>
<td>135</td>
<td>56</td>
<td>34</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>FH considered with precedent</td>
<td>97/187</td>
<td>33</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FH considered without precedent</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>22</td>
</tr>
</tbody>
</table>

Among the 50,286 sequenced participants, we identified 229 heterozygous carriers of 3 FH variants, corresponding to a total carrier frequency of 1/222 participants (Table 1). There were no cases of homozygous or compound heterozygous FH. Given that this prevalence estimate is based on a sampling of individuals within a single health care delivery system, it may be an overestimation of population frequency due to ascertainment bias. The MyCode cohort included 5,397 participants recruited from the cardiac echocardiography laboratory; the estimated prevalence of FH among these participants was 111, and the prevalence in other participants was 40/3,892 (42.5%) compared with 40/3,892 (42.5%) in the MyCode cohort.
The underlying reason for calculating the fraction of the mutation spectrum is to ask, *How many other APOB are there?* And we don’t have a right to the question, because we already have all the APOB from the beginning. There are no others. 19 is not half of an amulet, from which we can derive another half. 19 is the whole amulet: 19 probands ÷ the proband total of 19 = 1. And so 111 APOB molecular hits in the Copenhagen sample ÷ 1 equals 111 total APOB mutation carriers in the Copenhagen sample. FDB prevalence manipulation is extreme. With goosing, the prevalence is 1:118. Without goosing, the prevalence is 1:884. This is because there is no “proportion” of a spectrum to speak of, since the R3500Q/W make up the whole of the FDB spectrum found in the study. Here are the calculations of APOB *with and without LDLR added* into the denominators.

<table>
<thead>
<tr>
<th>Isolated ADH constituent</th>
<th>APOB with LDLR added (2nd report)</th>
<th>APOB without LDLR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proband Found</td>
<td>Total Probands</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

**Isolated ADH constituent**

**APOB with LDLR added (2nd report)**

**APOB without LDLR**

---

**Supplementary Table 2. Characteristics and genetic diagnosis of probands referred for genetic testing for familial hypercholesterolemia.**

<table>
<thead>
<tr>
<th>Capital Region of Denmark Tybjerg Hauge</th>
<th>Western Denmark Damgaard et al.</th>
<th>Southern Denmark Bruengard et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion period</strong></td>
<td><strong>Referral criteria</strong></td>
<td><strong>Referral criteria</strong></td>
</tr>
<tr>
<td>2007-2014</td>
<td>LDL cholesterol &gt; 5.0 mmol/L (&gt;4.0 mmol/L if age &lt; 16 years) and at least one of the following criteria:</td>
<td>LDL cholesterol &gt; 5.0 mmol/L (&gt;4.0 mmol/L if age &lt; 16 years) and at least one of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>1) Tendon xanthoma in patient or first degree relative.</td>
<td>1) Tendon xanthoma in patient or first degree relative.</td>
</tr>
<tr>
<td></td>
<td>2) First degree relative with LDL cholesterol &gt; 5.0 mmol/L in an adult or &gt; 4.0 mmol/L in a child &lt; 16 years.</td>
<td>2) First degree relative with LDL cholesterol &gt; 5.0 mmol/L in an adult or &gt; 4.0 mmol/L in a child &lt; 16 years.</td>
</tr>
<tr>
<td></td>
<td>3) Coronary or vascular disease before age 60 years in first degree relative, or before age 50 years in second degree relative.</td>
<td>3) Coronary or vascular disease before age 60 years in first degree relative, or before age 50 years in second degree relative.</td>
</tr>
</tbody>
</table>

**Supplementary Table 3. Participants in the Copenhagen General Population Study by carrier status of low-density lipoprotein receptor (LDLR) and apolipoprotein B gene (APOB) mutations.**

<table>
<thead>
<tr>
<th>LDLR mutation (n=63)</th>
<th>APOB mutation (n=111)</th>
<th>Non-carriers (n=97,924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 APOB + 123 LDLR = 142</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**123 inflates the denominator**

**How to identify persons with mutations causative for familial hypercholesterolemia: Screening of 98,098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217**

Motzke Isora, MD, PhD, DBc, PhD, 1, 2, 3, Gerald F. Wann, MD, PhD, DBc, 1, 2, 3. Tøjbyng Hauge, MD, DMSc, 1, 2, 3, and Jørn G. Nordestgaard, MD, DMSc, 1, 2, 3.
To use an analogy, imagine that a prison warden gets paid by the number of prisoners kept. We are in the early days of forensic science and there is a poorly understood crime. In fact, in a recent survey, less than 30% of detectives could recognize the crime from a case study. For the warden, this general ignorance is not a danger; it is an opportunity to "educate" those charged with apprehending criminals. He hires experts which use the credibility of forensics in a demonstration, not to expose gross errors when relying on circumstantial evidence, but only to prove that many of the real criminals are "getting off scot-free," knowing full well that detectives in the field don't have the requisite infrastructure and that they can and will only avail themselves of their inherited, poorly understood reliance on circumstantial evidence. (So ironically, the reason why so many criminals go free is because of the prevailing cultural reliance on circumstantial evidence.)

It was the expert's duty to correct the misunderstanding, and so to protect himself, he adds a verbal disclaimer, with euphemisms like, "limitations to circumstantial evidence," and using the word "caution" with the worst example of failed evidence imaginable, which was nonetheless used in his presentation as proof that large numbers of criminals are running free. (See Lancaster, PA on page 26). Culture is a fait accompli, and so the mild disclaimers have no effect on the prevailing use of circumstantial evidence. That brief disclosure aside, he returns to the call for action, "dangerous criminals are getting away with it" and then tells the detectives that "circumstantial evidence is standard practice and recommended." The prevailing cultural bias does its downstream work for the Warden.

In short, the warden engineers a social condition the outcome of which swaps out the difficult-to-find real targets and swaps in the easy-to-find innocent.
**Key Reports**

I invite the reader to *set aside* my analysis at any time and initiate an independent reconciliation of the following reports.

| **“1st Danish Report”** | | |
Table of Contents

“Higher Prevalence” is the key to Marketing Drugs ................................................................. 2
Outline through Analogies: ........................................................................................................ 3
Detailed Outline of Prevalence Strategy and Tricks ............................................................... 4
Key Reports .................................................................................................................................. 11
Table of Contents ....................................................................................................................... 12
Conflation of several diseases: .................................................................................................. 14
Likewise, FDB-as-R3500Q is not that different from established estimates .................................. 19
The Danish studies also conflated FDB (APOB) with FH (LDLR) ........................................... 22
The increase in prevalence is a false claim. ............................................................................. 23
Geno-mandering: Epidemiologists have taken a page from politicians’ Gerrymandering ........... 24
Geographic migrations do not erase genetic inheritance ......................................................... 25
Founder Effect inflates the outcome: The Amish community in Lancaster, PA ....................... 26
“Caution” is a self-interested disclaimer. .................................................................................. 27
1st report, a lower clinical standard = more “FH” .................................................................... 29
Lower standards and mathematical shenanigans ..................................................................... 30
A similar prevalence tactic: Injecting a sliver of inflated results ........................................... 36
Goosing denominators before calculation .............................................................................. 38
Goosing FH with FDB .............................................................................................................. 42
Goosing FDB with FH .............................................................................................................. 44
Good math is reversible; these numbers are not. ..................................................................... 49
FH LDLR and FDB APOB prevalence, without leveraging the denominator ............................... 52
Without “Cherry-picking,” the numbers return to estimates established by previous scientists ........ 55
In the strategy room, swapping patients ................................................................................ 56
First step: Exaggerated prevalence “proves” and leverages the urgency of “Underdiagnosis” ........ 57
Second Step: Use selection bias .............................................................................................. 60
Reconciling 1st & 2nd Danish reports: 1 page mathematical proof of the patient swap ................. 62
Reconciling 1st & 2nd Danish reports using the maximum & minimum numbers mathematically possible ................................................................. 63
Reconciliation of the 1st & 2nd Danish Reports, in greater detail .............................................. 64
Deductive ceiling: 1st report’s key number cannot be more than 25 ......................................... 66
The 2nd report serves as a “Rosetta Stone” for understanding the 1st report ............................... 67
What if we apply the 1st report’s method to the 2nd report’s data? ........................................... 69
Using the 1st and 2nd report methods on 1st report’s deductive ceiling .................................... 69
Estimates of the 1st report’s molecular hits which originally scored above the clinical cutoff ........ 73
Two different “FH” populations alternate between the two reports ......................................... 75
Regeneron’s Science magazine article supports my analysis of the Danish reports .................. 77
Weakest Link in my analysis of Danish reports is nonetheless strong ...................................... 77
Anatomy of the Publication Strategy ........................................................................................ 82
Selective publishing of a Selection Bias: .................................................................................... 82
Analogy: The Prison Warden who shouts “forensics” in order to prod others to their default reliance on circumstantial evidence .................................................................................. 83
Actuality: Big pharma uses genetic studies in order to prod others toward their default reliance on clinical scoring systems ............................................................... 84
Publication Strategy in Action: Push Clinical Diagnosis while shouting the alarm of “underdiagnosis.” ................................................................. 85
The FDA makes a clear rejection of Nonfamilial Hypercholesterolemia ..................................... 89
Unfamiliar terms give a margin for misunderstanding which common sense would never allow. ................................................................. 91
The fait accompli of Information Dependence ................................................................. 93
Evolution of Publication Strategies for Off-Label sales: ......................................................... 94
What the illusionist sees is not what the audience sees: phenotype versus genotype .................. 95
Conclusion ...................................................................................................................................... 96
Red Flags ....................................................................................................................................... 98
Citation Kiting: The industry’s “Authoritative” prevalence has no external, contemporary source. 98
Conflict of interest in the 2nd report? ................................................................. 104
Copenhagen Study Population Confusion. .............................................................. 105
2nd report Supplement, Table 5: population errors and confusion. .......................... 106
Observations .......................................................................................................... 107
Contingency table exposes the motive & 78% false positives................................. 107
Smoothly off-Label: The Trick to the 1st report is the basis for the Authoritative report ................................................................. 108
The Larger Issue: Pharma “cherry-picks” researchers, corrupting scientific procedure ................................................................. 113
Scientific culture precedes science .................................................................... 115
Appendix .................................................................................................................. 116
Review of key scientific reports ............................................................................. 116
Other Significant Reports ....................................................................................... 118
Terms ....................................................................................................................... 120
Key Data from the Danish reports (Authoritative report has no fundamental data of its own) ........................................................................................................... 122
Corrigendum and 1st report: key numbers .............................................................. 123
1st report false positive %; the source for the Authoritative report ......................... 124
FH and FDB conflation: Introduction to the confusion ........................................... 125
Cascade Screening in the USA is not practiced ..................................................... 128
Evidence that half of the APOB count may be irrelevant ........................................ 129
Synonymous usage: p.Arg3558Cys = Arg3531Cys and R3531C. ............................... 131
Synonymous usage: p.Arg3527Gln = R3500Q and Arg3500Gln .............................. 132
Unanswered Email to Corresponding Author ....................................................... 133
Research derived from the Netherlands: founder effect is irrelevant to general prevalence rates .................................................. 134
Denmark’s “intermediate” FH-FDB prevalence is somewhere between regions with full founder effect and melting pots such as Germany and the USA ................................................................. 137
FDB APOB has unusually high prevalence in Northern and Central Europe .......... 138
Lars Anderson wrote a very accessible article on APOB prevalence in Europe and Lancaster, PA ................................................................. 139
Conflation of several diseases:

(For background information regarding the confusion between FH and FDB, see page 125.)

How can one increase a prevalence rate without having to find more people?

*Linguistics.*

It is a *linguistic strategy*, not a scientific study. The claim of higher prevalence is *false*.

Again, the issue here is not whether or not those with other diseases should be given medication indicated for FH, or whether all should now be called “FH” or whether the former disease names should be discarded. That’s a question for the medical community and the FDA. What concerns us here is whether or not new people have been found. Is there a higher prevalence than previously thought? No, there is not. That is false and a misrepresentation of both the gravity of the situation and the addressable market of the drugs in question. Once the linguistics is understood and the relevant math laid out in rows and columns, Regeneron’s prevalence estimate for FH-as-LDLR is actually lower than the established rate. Other diseases, as before, have their own prevalence. If we decide to blend them linguistically under one name, we do the required math. That’s it.

Imagine that I count 200 people. 100 of them have LDLR mutations and are in a room with “FH” painted on the door, and the other 100 have APOB mutations and are in another room with “FDB” painted on its door. If I herd the 100 people from the “FDB” room to the “FH” room, and then whitewash over “FDB,” leaving that room empty, then do I have 100 more people than previously thought? No. I still have a total of 200. Do I have more “FH” than previously thought. Perhaps. Sort of. But it would be the expansion of the previous linguistic definition of “FH” into something new. It would not however be a “discovery” in the explorer’s or scientist’s sense of the term, certainly not the discovery of more diseased patients. Anyone who thinks otherwise would have serious difficulty barring a professor of linguistics from entering the debate. Inside the old room with “FH” still painted on the door we still have 100 with LDLR mutations and 100 with APOB mutations.

Why do this? There is some confusion about what FH is and what it isn’t. And one will find FDB and FH both referred to as FH. Strictly speaking, however, FH and FDB are two different inherited diseases. (The emphasis is mine.)

*FDB is a disorder which is clinically and biochemically indistinguishable from familial hypercholesterolemia (FH), a disease caused by LDL receptor gene mutation. This was demonstrated by the fact that approximately 3-5 % of FDB patients are incorrectly diagnosed as FH (Weisgraber et al. 1988). However, reviews dealing with the comparison between FH and FDB homozygotes and heterozygotes showed that hypercholesterolemia, which arises from the genetic condition, is generally milder and more variable in FDB (Miserez and Keller 1995). Furthermore, the development of atherosclerosis is delayed in comparison with FH patients (Brousseau et al. 1995, Tybjaerg-Hansen et al. 1998, Če.ka et al. 2000). ~ “Major Apolipoprotein B-100 Mutations in Lipoprotein Metabolism and Atherosclerosis,” M. VRABLÍK, R. ČE.KA, A. HOŘÍNEK*
The Regeneron report, like the Danish reports, blends FH and FDB due to available linguistic ambiguity and then refers to the natural mathematical result as a larger FH prevalence count.

The established prevalence of FH-as-LDLR mutation is 1:500. Of FDB-as-APOB mutation, it is 1:1,000. If I combine FH and FDB, I mathematically derive a prevalence of 1:333. If I call these combined patients “FH,” have I really found more patients or have I simply put two formerly distinct diseases under a single umbrella-term, “FH,” which then requires that I follow through with the required math? What if I add in FH3, which refers to PCSK9? I can also add in a controversial APOB mutation into FDB. P.Arg3558Cys, AKA, R3531C, Arg3531Cys, is found to interfere with the cholesterol process, in the lab. In the living, however, it has been said to be too weak to be included.

Vrablok reveals the point of confusion: in vitro versus in vivo. (Emphasis mine.)

“These are mutations leading to amino acid substitution at positions 3500 (R3500Q and R3500W) and 3531 (R3531C) that have been shown to decrease the binding affinity of apoB-100 in vitro. However, only the former mutations have been unequivocally demonstrated to cause hyperlipidemia in vivo.” ~ VRABLØK

Here is Tybjaerg-Hansen and Nordestgaard (who will later co-author the Danish studies, with financial influence from Big Pharma):

“In contrast, the Arg3531Cys mutation, which is just as common, is not in itself associated with hypercholesterolemia or an increased risk of ischemic heart disease.” ~ TYBJÆRG-HANSEN, et al.

Here is the title of a study which focused on this issue:

“R3531C mutation in the apolipoprotein B gene is not sufficient to cause hypercholesterolemia.” ~ Rabes JP, et al.

In short, p.Arg3558Cys, AKA R3531C, was not counted in previous FDB prevalence estimates. (See page 21.)

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3 See page 129 for these and other references to the exclusion of p.Arg3558Cys, AKA, Arg3531Cys and R3531C. See page 131 for p.Arg3558Cys equivalents.
Below, with Dr. Rader’s responsible breakdown of the specific prevalence rates, we can clearly see the established rates of the individual diseases. We’ll combine them and do the required math.

We can now say, “Our addressable market is twice what we previously thought it was.” How clever. This is a culturally broader definition of “FH,” not an addition of newly discovered patients. The total of FH + FDB + FH3 + p.Arg3558Cys does not change and neither do any of these constituents when teased back out. There is nothing new here. Before the necessary math, FH-as-LDLR was 1:500 and after the math, FH-as-LDLR is still 1:500. Here’s the recent study funded and staffed by Regeneron, published in Science magazine.

Ironically, in the very act of conflating Non-LDLR with LDLR, and calling the result “FH” the prevalence for the previous LDLR-based definition of FH is actually supported: 1:500. (50,726 ÷ 98 = prevalence of 1 in 518.) In the act of declaring what is actually a mere linguistic victory, the old, established prevalence of FH-as-LDLR is silently supported. 4

Regeneron’s “new” prevalence, with conflation, is between 1:222 and 1:256. The “old” prevalence, after factoring in that conflation, is 1:232. The new prevalence is not really different from the old prevalence.

4 The established FDB prevalence is also silently proven. See page 19.
The difference in Regeneron’s “higher” prevalence is not found in an addition of new people, but in the subtraction of a necessary explanation of this linguistic maneuver.

This is not a prevalence study. It is a linguistic shell game. But the FH numbers deteriorate even further. Once we remove the cohort inflated by ascertainment bias (a form of selection bias), we see that what Regeneron declares as a higher prevalence, is actually lower, due to two factors.

**First, let’s look at what was disclosed.** A 6,747-cohort inflated by selection bias was inserted into the results. Its prevalence was almost twice that of the total results’ prevalence. Thus, after the removal of the bias, the prevalence comes down to 1:256.

Linguistic conflation of the various diseases with their totaled prevalence calculated from established rates (I use Regeneron’s own results for p.Arg3558Cys):

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>FH variant positive/total</th>
<th>Estimated prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DiscovEHR participants</td>
<td>229/50,726</td>
<td>1.22</td>
</tr>
<tr>
<td>Participants recruited from cardiac catheterization lab</td>
<td>57/6,747</td>
<td>1.138</td>
</tr>
<tr>
<td>Participants recruited from other sites</td>
<td>172/43,979</td>
<td>1.256</td>
</tr>
</tbody>
</table>

Net result: **1:256**

The result of this subtraction is **1:256** Per Million, basic math required by the linguistic conflation, using the already established rates yields 4,310 and this is clearly higher than the 3,906 in Regeneron’s results. Even if we give Regeneron’s and the established prevalence a 10% margin of error, the resulting parity alone shows that the claim of higher prevalence is false. Regeneron’s result would be precisely what was previously thought, not higher.

**Second, we’ll look at what was not disclosed:** the breakdown of APOB-to-LDLR after the 6,747 are backed out of the results. It is highly likely that the LDLR will be removed at a much higher rate than the APOB, further distorting the already inverted ratio of APOB-to-LDLR.

Let’s run through the reasoning. In this case, we begin with a biased total and we are calculating the LDLR count after the removal of the bias. To illustrate the force at work here, consider the following example. If I give a customer a bag of pure popcorn and another bag, half-popped, without a detailed explanation, then I can tell the customer that the prevalence of un-popped kernels of both bags

4,310 > 3,906

This assumes the Amish were not overrepresented in this group.
combined is 1:4. If I then take back the bag with pure popcorn, the prevalence of un-popped kernels in the remaining bag is 1:2. Without an explanation of the breakdown in the original bags, the customer will naturally believe that the prevalence of un-popped kernels at 1 in 4 still applies to his snack. It does not. The force of the selection bias, in reverse, increases the proportion of un-popped kernels in the customer’s possession, and the customer is left, so to speak, holding the bag.

This same force is exerted on the Regeneron prevalence estimate when one of the acknowledged selection biases is reversed back out. The health consequences of the mutations in question are more variable than big pharma wants us to believe. The clinical scoring systems themselves, due to this variability, result in an inherent selection bias. As we can see below, the passing scores are in actuality a minority of total mutations and of those that do pass, there is a predominance of LDLR over APOB. This is because, as is widely known, APOB is weaker than LDLR.

The 6,747-cohort inflated by selection bias was inserted into the Regeneron results. Although there is a different circumstance behind this selection bias, because both instances of the bias filter out weaker cases both will result in collecting the more severe mutations, and that would be mostly the LDLR. So the proportion of LDLR-to-APOB between the two instances of bias will differ, but precedent being our guide, the principle will hold: the stronger LDLR will predominate, and the weaker APOB will be far less represented. Consequently, in the net 43,979, there will be a disproportionate loss of LDLR from the results as this LDLR-inflated group is taken away. Prevalence for FH-as-LDLR will be even lower, and the APOB/LDLR ratio will be even more at odds with other studies. With this biased cohort in place, FH-as-LDLR prevalence was 1:518 – in line with established estimates. After removing this biased cohort, it follows by deduction, given the preceding points, that Regeneron’s study does not actually have a higher FH-LDLR prevalence than the established 1:500, and not even equal, it is actually lower than previously thought.7

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6 “Both instances” and “two instances of bias” = the 6,747-cohort in the Regeneron study and the bias inherent in DLCN scoring as demonstrated in Benn’s 2nd report.

7 See also page 36.
Likewise, FDB-as-R3500Q is not that different from established estimates

Conflating R3500Q with controversial R3531C does not increase FDB-as-R3500Q.

R3500Q is also known as p.Arg3527Gln, and R3531C is also known as p.Arg3558Cys. (See pages 132 and 131.) For the paragraphs below I will defer to Regeneron’s use of p.Arg3527Gln and p.Arg3558Cys. Elsewhere in my report I will defer to the 1st and 2nd Danish report’s synonymous usage of R3500Q, in comparison with which I will use R3531C.

FDB is usually restricted to p.Arg3527Gln. Previous studies of FDB prevalence have not used p.Arg3558Cys. There is no doubt that when it comes to p.Arg3558Cys, there is some in vitro evidence suggesting FDB. However, it has been determined by many scientists that the p.Arg3558Cys is not sufficient to constitute FDB, in vivo. Like the FH and FDB conflation demonstrated in the preceding chapter, an explanation is lacking here as well.

Traditionally, prevalence for FDB-as-p.Arg3527Gln is between 1:1,000 and 1:1,250. In this Regeneron associated study FDB-as-p.Arg3527Gln is 50,726 ÷ 56 = prevalence of 1 in 906. Regeneron’s FDB-as-p.Arg3527Gln prevalence rate appears to be slightly higher than the established rate. However, influences of selection bias are present, and two of them are serious. First, this result enveloped a region known to have the highest p.Arg3527Gln prevalence in the world, due to founder effect. (See page 26.) Second, the result was from 98.4% whites of European descent, a group known to have higher prevalence of this APOB mutation than the general population. (See page 25.) Once these biases are removed, it is likely that the prevalence will be equal to or lower than the established rate.

Adding the p.Arg3558Cys into a prevalence count feels more like slipping a Canadian quarter into a roll of US coins and then handing them all over to the practical assumptions of a bank teller. If one insists that Canadian quarters should be counted, the controversy should be addressed openly. The fact that a culture may unwittingly circulate foreign coins does not mean that the bank is going to accept them. From the start, customers and merchants alike should be informed, and bankers should be consulted.

Likewise, where is the FDA on this? Is FDB “FH”? Is p.Arg3558Cys “FDB”? Does the medical community even know the elements to the debate? How could they? Big Pharma is in control of the publication strategy, and formerly distinct diseases have already been conflated into “FH.” And now we see the same sort of conflation within FDB: a mutation which had previously not been included in FDB prevalence counts is suddenly included. Can I really compare two prevalence studies whose constituents are not identical?

For example, if Study A declares: “10 horses are under a tarp,” but Study B stretches that tarp further over 10 zebras and calls all of them, “20 horses,” the number of horses has not increased; the number of zebras has not increased, and the total of both has not increased. There is no news here. A claimed “higher prevalence of horses” is really just definition stretching, not discovery. It is simply a linguistic and mathematical manipulation. If p.Arg3558Cys had not been counted before, but are now, then the issue belongs to a linguistic reclassification and an incidental mathematical adjustment. The new accounting should be out in the open. There should not however be a claim that more people were found:
separately identified groups have been joined together under one of their names – incidentally, the one most likely to be indicated by the FDA for drug sales: “FH.” That’s it. There should have been nothing new here besides the necessary math after stretching the linguistic definition. But no, FH is first conflated with FDB, which itself is a conflation of the heretofore counted APOB with heretofore uncounted APOB.

Again the issue of whether to include or exclude \texttt{p.Arg3558Cys} as an FDB mutation is an issue for the medical community and the FDA to decide. \textit{The violation I outline here is with simple linguistics and math. Stretching the definition of FDB over \texttt{p.Arg3558Cys} and comparing the result to previous studies that did not stretch the definition must be accompanied by both a detailed explanation and a routine breakdown of the mathematical adjustment.} FDB-with-\texttt{p.Arg3558Cys} is not an increase over FDB-without-\texttt{p.Arg3558Cys}; it is just a bad rhyme – or more like a \textit{pun}, where two meanings are triggered by a single word, “FDB” ... but then again, it is unlike a pun in that \textit{in this case} the listener is not supposed to “get it.”
APOB R3531C were not counted in previous prevalence studies:

**APOB R3531C, AKA, p.Arg3558Cys, were not counted in previous prevalence studies.**

For the FDB prevalence estimates of 1:1,000 and 1:1,250 only **R3500Q, AKA p.Arg3527Gln**, was counted.
The Danish studies also conflated FDB (APOB) with FH (LDLR).

For example:
The increase in prevalence is a false claim.

Here is Michael F. Murray, Geisinger director of clinical genomics. He is listed on the Regeneron paper as the corresponding author.8

“The study shows us that FH is about twice as common as it was once thought to be ...” 9

Here is the Regeneron-funded study’s lead author,” Noura Abul-Husn, of the “Regeneron Genetics Center,” using almost the exact same string of words: “twice as common as it was thought to be.”

These statements are false. The results are less than previously thought. In reality, it is only the pharma-definition of FH which is not what it was commonly thought to be. The only result greater than previously thought is the length to which pharma has gone to stretch community perceptions.

Now, upstream academics “educate” downstream medical practitioners with statements of new and improved FH prevalence. And it is effective because ....

“Fewer than 30% of cardiologists surveyed recognized FH when shown a National Lipid Association (NLA) case example.” ~ Dr. JoAnne Foody, with editorial assistance. The 2011 survey cited was funded by Sanofi, Regeneron partner.10

If an argument can be made that these separate diseases are serious enough to be included as FH, meaning that we overcome the argument that most APOB are much weaker than LDLR, then we are still left with the deception that “FH is twice as common as it was thought to be.” The prevalence of each of the constituents has not changed and in fact prevalence of LDLR, pure FH, is less than previously thought in the Regeneron study.

8 I emailed him several detailed questions about the breakdown of LDLR and APOB after the cohort with selection bias was removed from the results. I received no reply. See page 133 for a copy of the email (and a hypothetical wager I would make on the answers to my questions).
9 PR by Regeneron Genetics Center, and others, announcing the above-mentioned article in Science. “Geisinger and Regeneron study finds life-threatening genetic disorder is substantially underdiagnosed,” Dec. 22, 2016
10 “Familial Hypercholesterolemia: An Under-recognized but Significant Concern in Cardiology Practice,” JoAnne M. Foody, MD, FACC, FAHA
Geno-mandering: Epidemiologists have taken a page from politicians’ Gerrymandering

- **Gerrymandering** is where politicians have the power to draw the borders around precisely those voting districts which maximize the outcome of a future election in their own favor.

- **Geno-mandering** is where researchers have the power to draw the borders around precisely those geographic regions which maximize prevalence of a genotype in the favor of Big Pharma.

Previous prevalence studies funded by big pharma focused on two countries: Denmark and The Netherlands.

- **Page 134**: Previous research in The Netherlands concluded a *founder effect* — an anomaly in genetics where *concentrations* of mutations occur.\(^\text{11}\) The Netherlands cannot reasonably be used as a proxy for a heterogeneous population such as the USA.

- **Page 137**: Denmark’s FH mutation spectrum is considered to be *intermediate*, somewhere between that of a region with founder effect and a melting pot such as Germany.

- **Page 138**: Additionally, for FDB (APOB carriers), prevalence is outsized among those in Central and Northern Europe.

Neither of these two countries can reasonably be used to extrapolate prevalence to a general population, the world, or the USA. Not for FH-as-LDLR, not for FDB-as-R3500Q/p.Arg3527Gln.

The studies in Denmark were of “whites of Danish descent.” At the end of successive research papers, a later *citation* of the source is regarded as *the source itself* and now this self-same *restricted* population is declared to be the “general population.” This is another example of what I call “citation kiting.”\(^\text{12}\) It enables a “conclusion drift.”

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\(^{11}\) For more on the industry’s use of The Netherlands and founder effect, see page 134.

\(^{12}\) See “Citation Kiting” regarding these reports on page 98.
In the above, only Benn, et al, performed a prevalence study. The following Nordestgaard report conducted no prevalence study but simply cited Benn, while opting out on the word “Danish” in the title, claiming instead the “general population.” Then Cuchel, by citing only Nordestgaard and not the actual source, can take Nordestgaard’s title of “general population” and omit mention of Benn’s original disclosure of “all whites of Danish descent.” Now as if representative of the USA, we move from a very specific slice of demographics, to something which represents all of the USA, with one and the same source population sponged out of the prevailing literature: whites of Danish descent.

Geographic migrations do not erase genetic inheritance

➢ Relative to U.S. demographics, the 98.4% whites of European descent in Regeneron’s Pennsylvania study are more similar to, than different from, the “whites of Danish descent” in the Danish studies.

Now Regeneron funds a study here in the USA. This is a chance to confirm the relevance of the FH population studies performed in Denmark and The Netherlands and quell suspicions that strong and intermediate influences of founder effect were at play. They only needed to target a broader, more representative demographic.

So where does Regeneron perform the study? In Pennsylvania, enveloping a region with the highest APOB founder effect in the world, and somehow managing to test 98.4% whites of European descent.

“This was suggestive of a single mutation transmitted from a common ancestor through the population, with endogamy and genetic drift accounting for its high frequency in the Amish. A prevalence of 1 in 8–9 participants, the highest frequency for APOB p.Arg3527Gln yet recorded, coupled with a strong association with both LDL-cholesterol levels and coronary artery calcification scores, establishes a clear case for the benefits of community screening. ~” Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution Khemanganee E. Liyanage, et al. [Emphasis mine.] See also page 139.

Questions: Was this an accident? Did the researchers specifically choose regions which did not represent a broader demographic? Or, were non-whites simply selected out of the study? I ask because the raw database begins with 3% Black/African American, but the selection procedure reduced the representation to 1% for the study, while at the same time increasing the White representation from 93% to 98%. This will necessarily influence the APOB count due to the over presence of the White population, which the authors said were mostly of European descent.
With disclaimers secured in the report, the PR nonetheless blatantly claims an increase of prevalence in the general population, but this was actually a study narrowed to a group of white European descendants.

“Results of the new study found many undiagnosed cases of FH and helped to define the extent of FH in the general population and the extent to which it is systematically undertreated.” ~ Press release: Geisinger and Regeneron study finds life-threatening genetic disorder is substantially underdiagnosed; Dec. 22, 2016

So any good explanation for the exclusion of non-whites nonetheless begs the question, why wouldn’t researchers ensure a demographic representative of the whole USA?

**Founder Effect inflates the outcome: The Amish community in Lancaster, PA**

Regeneron mildly discloses the use of Lancaster, PA. They mention the inclusion of the Amish, as if it were cautionary and not a disqualification from extrapolating the results to the general population. Here is an excerpt from the report:

“Conclusion:

*Underdiagnosis and undertreatment of FH continue to be a concern ....

.... the prevalence was 1:256, in line with more recent estimates of 1:217 in Denmark and 1:319 in the Netherlands. Our assessment of FH prevalence in a U.S. Health care system using this methodology supports the claim that there is significant underdiagnosis of this condition. Whether our estimated prevalence of FH variants in our patient population, largely a stable regional health care population in central Pennsylvania, is generalizable to other U.S. patient populations remains to be determined. We caution that extant familial (and cryptic) relatedness in our study
population could result in overestimation of a given FH-causing allele that is rare in the general population, but segregating in family members. For example, our study population was enriched for APOB p.Arg3527Gln, which is known to be common in individuals of Amish descent in Lancaster, Pennsylvania.” ~ Science (sciencemag.org) “Genetic identification of familial hypercholesterolemia within a single U.S. health care system,” Dec. 2016, Dewey et al. and Abul-Husn et al. 10.1126/science.aaf6814, p. 10.1126/science.aaf7000

“Caution” is a self-interested disclaimer.

➢ The exclusion of any population with founder effect was required and the inclusion invalidates the results.

Instead of highlighting a serious objection, the study euphemized the influence of founder effect with the words, “enriched for APOB.” The Amish have the highest p.Arg3527Gln prevalence on record.13 And with the word, “Caution,” this disclosure seems more likely to mitigate objections by this pre-emptive mentioning, than to fully disclose the irrelevance of this study. It takes the edge off of legal and professional criticism. The inclusion of the Amish population and focus on whites of European descent, not to mention the exclusion of the non-whites, warrants a much stronger treatment in Regeneron’s paper than is present.

From Europe to the USA ... to study ... the same descendants?

All the way from the mutation-rich white Europeans, we move our research to the USA, and then we still study ... whites of European descent? ... and only coincidentally, enveloping regions on both continents known to be influenced by founder effect?

As far as bias and absence of bias is concerned ...

- There are more similarities than differences between the white Europeans in Europe and the white European descendants in Pennsylvania.
- There are more similarities than differences between founder effect in The Netherlands’ and founder effect in Lancaster, PA.

With this new Pennsylvania study, the important questions from the European studies are not eliminated; they now require greater emphasis. Why Pennsylvania? Why 98.4% Whites of European descent? Why include a region with known founder effect? Why not choose a region within the USA that is representative of the demographics of the USA as a whole? Or at least, why not secure a representation of the whole USA through inclusion of a random selection of the non-whites already present in the database of “GHS active patients”?14

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13 Emphasis mine: “This was suggestive of a single mutation transmitted from a common ancestor through the population, with endogamy and genetic drift accounting for its high frequency in the Amish. A prevalence of 1 in 8–9 participants, the highest frequency for APOB p.Arg3527Gln yet recorded, coupled with a strong association with both LDL-cholesterol levels and coronary artery calcification scores, establishes a clear case for the benefits of community screening.” ~ Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution, Khemanganee E. Liyanage, et al.
14 See screenshot of “Table 1” on page 26.
Otherwise, stop claiming relevance to the “general population” in PR. And remove the blanket-statement that “FH is twice as common as it was thought to be” -- a fuller disclosure translates that statement into a truism: **An uncommon approach to FH prevalence yields uncommon results.**

(For more on the industry’s use of The Netherlands and founder effect, see page 134.)
1st report, a lower clinical standard = more “FH”

**Analogy, growing apples up to the speed of ridicule:** A farmer wanted to sell more apples but was limited to a single tree. It was a lot of work for a modest profit. But one day a tourist came to the edge of his farm, pointed at a tomato and asked, “how much is that apple?” At a distance of 10 yards, the farmer learned, customers could not tell the difference between some tomatoes and most apples. So he put up a fence, separating the table of fruit from his customers by 10 yards. He sold 5 tomatoes as apples for every 10 real apples sold. If at 10 yards tomatoes could appear to be apples at a ratio of 1 for every 2, how many more “apples” would he sell if he separated the customer from the fruit by 20 yards? The difference between 10 yards and 20 yards, was the addition of 2 tomatoes for every 1 apple. He decided to set the distance at 30 yards, but told his customers that they were standing 20 yards away. Now according to his math, the new “fruit” added to the previous results would be 3 tomatoes for every apple. But at this point the customers threw up their hands, laughed and walked away. He apologized and said that it wasn’t that he misspoke; he simply measured incorrectly. He had accidentally measured 30 yards instead of the 20 yards he told them. He then matched up the measurement used in the actual evaluation with the message he gave his customers: 20 yards. Nonetheless, he still mixed this year’s tomato harvest with this year’s apple harvest and put up a sign that read: “We have more apples than previously estimated.” No one asked, why 20 yards and not 10 or 15? And then along came a prospective buyer.

- **Prospective Buyer:** So how many apples do you have there?
- **Farmer:** It all depends sir. How far can you step back without feeling ridiculous?

**Review of actual case:** The pharmaceutical industry wants to sell more of its drugs, but it is limited to those who inherited a specific LDL-R mutation: FH. It was previously held among the scientific community that FH has a prevalence of 1:500. That would provide a modest profit. However, it is widely known that in clinical analysis mistakes are often made. Many of those who are determined by a clinical scoring system cannot actually be found to carry a mutation when subjected to molecular testing. The clinical scoring system only tells a doctor that those above a given detection point look like they might be carriers of the mutation. For example, Damgaard, et al, performed a study of those who scored in the top clinical category and found that 1 in 3 could not be found to have a mutation. As we move down the scoring system, loosening standards, the second lower category showed 2 in whom a mutation was not found for every mutation found. That’s 2 out of 3. Within this category, we have flipped the risk-benefit ratio on its head by lowering the diagnostic standard a single notch. The next lower category has a failure rate of 78%. This is what the authors did. They not only lumped the first two categories together, which then averaged 50%, but they also took a slice of this lower category with its 78% failure rate and blended it in, declaring a prevalence rate of 1:137 – extremely high. Forced, or unforced, the authors later issued an apology and correction. They had printed “6” as their DLCN cutoff point, but actually used 5 on the data underlying the printed result. It wasn’t that the text contained a typo; it’s that the greater part of their labor in crunching the data used the wrong number. Essentially, they put “cutoff 6 = prevalence of 1:137” on the table, while under the table they had arrived at 1:137 by using the cutoff point of 5. The “Corrigendum” essentially took out the slice from the lowest of the three categories, but still blended the other two. What were the reasons for the adjustments? Why one number and not the other? The clinical cutoff chosen appears to be arbitrary. Where was the concern or mention for false positives that are always a consideration with clinical screening? If one lowers the standard, wouldn’t one take it for granted that there will be more errors? ... more false positives in the result? Where is the accounting for this?

- **Patient, Doctor, and Investor:** So what’s the appropriate clinical detection point to determine FH?
- **Industry and Scientist:** It all depends sir. How far can you lower the standard without feeling ridiculous?
**Lower standards and mathematical shenanigans**

In the 1st Danish report, patients are derived by *increasing* inaccuracy. Of course, if I *paint a larger* bull’s-eye over the target, I will have more “hits.” Likewise, if I lower the standards for patient selection, I will find more “patients” ... because I make more *unacknowledged* errors.

Both the Regeneron and Danish reports inserted inflated groups into the underlying data, which *spiked* prevalence results. In the Regeneron example, an anomalous concentration of genuine carriers was inserted into the results. (See their explanation on Ascertainment bias and their inclusion of Lancaster, PA.) With the 1st Danish report, the larger instance of inflation consisted of false positives. How this inflation took place in this Danish report was suspicious.

The basis for the industry’s Authoritative report was purported to be this 1st report. The authors used lowered standards of diagnosis to reach a prevalence of 1:137. This tripled the established prevalence estimate.\(^\text{15}\)

It was previously held among the scientific community that FH has a prevalence of 1:500. It is also widely known that in clinical scoring systems mistakes are often made. A passing score only tells a doctor that those above a given cutoff point *look like* they might be carriers of a mutation. However, many of those with a passing score cannot actually be found to carry a mutation when subjected to genetic testing.

The standard DLCN clinical scoring system categorizes results as follows:\(^\text{16}\)

<table>
<thead>
<tr>
<th>Classification of HeFH</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable</td>
<td>6-8</td>
</tr>
<tr>
<td>Possible</td>
<td>3-5</td>
</tr>
</tbody>
</table>

Damgaard, et al,\(^\text{17}\) performed a genetic study of those who scored in the top clinical category and found that roughly 1 in 3 could not be found to have a mutation, 37% of those categorized as “definite HeFH.” That’s with a score of over 8. What happens if our cutoff is 6?

<table>
<thead>
<tr>
<th>Classification of HeFH</th>
<th>Percent which were <em>not</em> found to have a known mutation after molecular testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>37%</td>
</tr>
<tr>
<td>Probable (6 or over)</td>
<td>65%</td>
</tr>
<tr>
<td>Possible</td>
<td>78%</td>
</tr>
</tbody>
</table>

As we move down the scoring system to a cutoff of 6, loosening standards, the second lower category showed 2 in whom a mutation was not found for every mutation found. That’s 2 out of 3. As far as a pharmaceutical company would be concerned, a move to scores between 6 and 8 flips the risk-benefit ratio on its head. There are *more* patients without an identified mutation than there are those with identified mutations. If this data holds and if risk-benefit ratios are of some value, why would I choose to

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\(^{15}\) This new estimate will be trimmed back to a “double” in the Authoritative report.

\(^{16}\) Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease; Consensus Statement of the European Atherosclerosis Society. Nordestgaard, et al.

\(^{17}\) The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population: Dorte Damgaard, et al.
add in the “Probable” category? Why use a cutoff of 6 and not >8? ... or at least provide some explanation for opting for lower standards?

And the next lower category, “Possible,” has a failure rate of 78%. The 1st report did not just lump the first two categories together, which, using Damgaard’s results, would then average 50%; the report also took a slice from this lower category with its 78% failure rate and blended it in, declaring the prevalence rate of 1:137. As previously pointed out, this tripled the established estimate.

➢ If we lower the standards for accuracy do we end up with more carriers of LDLR mutations or do we disproportionately inflate the count with false positives?

But let’s look at the way that this slice was included in the results. On page 1, we read: “Main Outcome Measures: FH (definite/probable) was defined as a Dutch Lipid Clinic Network score higher than 5.” Higher than 5 is 6, and 6 is the traditional number. This is the first reference to 6 as the floor for the “Probable” category.

On page 2 of the 1st report, the cutoff point for the “Probable” category was said to be the industry standard, 6.18 And we see that the category for “Possible” already has a claim to 5 for its ceiling, so the next category up must begin with 6. These are the second and third references to the number 6 as the floor for “Probable.”

The Supplementary Table 1, also puts the cutoff for “Probable” FH at 6. And Possible, again, has a ceiling of 5, leaving the floor for the next category up as 6. These are the fourth and fifth references.

---

But straddling pages 3 and 4, in the “Results,” this floor is both 5 and >5 in the same sentence. Which one was used for the report? Which one was in error? For a cutoff point, >5 should be 6, and ≥5, would be 5. But then again, the report combined “Definite” and “Probable” for the result of 1:137 and here the explicit floor for the “combined” categories is >5 ... which is 6. This is the sixth reference for 6 as the floor, and this is the first and only reference to 5. And we note that 5 is only mentioned with the floor for the uncombined “Probable.” This means that every reference for the combined result is to 6. What would a knowledgeable professional think upon a casual reading of this text? ... especially given that “6” is already the standard.

We again add to this the fact that the range for the next lower category, “Possible,” is again explicitly recorded as 3 - 5 points. And to say it again, since the ceiling for “Possible” is 5, the “probable” category cannot also use it without double-counting patients. By process of elimination, “Probable” must be 6. This is the seventh reference to 6.

When I initially read the 1st report, the Corrigendum did not yet exist. I took the single mention of 5 as the typo, and not the other seven references to 6. I am confident that other readers did too. But if this cutoff of 5 was just a typo, then the results would not have actually been derived from the cutoff of 5. But they were. We later learn, after the Authoritative report cites this 1st report, that the actual cutoff was not the oft-mentioned 6, but the once-mentioned 5. Why? The standard cut-off was 6.

Here is the table from the correction:

<table>
<thead>
<tr>
<th>Table 1. Corrigendum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Unlikely FH</td>
</tr>
<tr>
<td>Possible FH</td>
</tr>
<tr>
<td>Probable FH</td>
</tr>
<tr>
<td>Definite FH</td>
</tr>
</tbody>
</table>

They had printed “6” as their DLCN cutoff point, but actually used 5 on the data underlying the printed result. It wasn’t that the “6” was a typo; it’s that the greater part of their labor -- crunching the data -- used the wrong number: 5.

Was this an accident? Let’s review the facts. In the 1st report there were seven references to 6 being the floor for the “Probable” category. There was only one reference to 5. Why would we take that single reference as correct and the other seven as the typos? Especially when we remember that 6 is the well-known, widely
published standard cutoff for “Probable.” We expect an explanation for deviance from the standard. The off-text calculation used 5 as the floor, and this is a break from the standard of 6, and so even if the number “6” were typed or implied incorrectly, 7 different times, we would still expect some compensatory references in the general text regarding the novel use of 5. For example, if a mechanic built a non-standard 7-cylinder engine but accidentally painted the expected “V8,” meaning 8 cylinders, on the hood of the finished car, we would still expect some discordant language in his description of the odd 7-cylinder engine he actually built — and who builds a 7-cylinder engine and doesn’t talk about the novelty? Likewise, there was no explanation in the 1st report for having broken with the DLCN standard and for using the nonstandard, unpublished 5 under the printed text of “6.” There were four authors.

Are we to believe that the choice of a non-standard cutoff point, with the key leverage over the mathematical outcome, endured a long, sustained error? Who could spend the central part of a labor with the wrong number of cylinders? It doesn’t sound right: “The ‘V8’ I painted on the hood of the car was not the mistake. I accidentally built an unusual 7-cylinder engine.” As far as FH is concerned, the difference between 6 and 5 was the difference between doubling and trebling the established prevalence rate.

This is the state of affairs when the Authoritative report cites the 1st report as the source for a doubled FH prevalence. In the Authoritative report, there is no specific mention of using the number 6 in the text while using 5 in the off-text math.

And this is why the results do not match up between the Authoritative report and its purported source, this 1st report: the Authoritative report simply cites this 1st report, but prints different results. The criteria used in one is not the criteria used in the other. The only remaining actual source for the Authoritative report, since the corrigendum does not yet exist, is a personal communication in a caption to an illustration with the lead author of the selfsame Authoritative report. It is essentially a self-citation, by word of mouth. An “error” is vaguely acknowledged as a “slight overestimation.” The difference between the new denominator, 223, and the old denominator of 137 is 63%.

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19 Although the 1st report actually trebles the rate, the caption in the Authoritative report “corrects” the number, resulting in a double, so to speak.

20 Regarding these reports, see “Citation Kiting” on page 98.
There is however a later apology for having used the cutoff of 5 off-text while predominantly using 6 in the text. The authors issued a “Corrigendum.” In the move from 5 to 6 as the off-text cutoff, they thus took out the slice from the lowest of the three categories used, but still blended in the other two categories.

**Corrigendum**

In the article “Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication” by Marianne Benn, Gerald F. Watts, Anne Tybjærg-Hansen, and Børge G. Nordestgaard (Clin Endocrinol Metab 97:3956–64, 2012; doi: 10.1210/jc.2012-1563) the authors have made an error during classification of study participants according to the Dutch Lipid Clinic Network criteria for diagnosing familial hypercholesterolemia (FH). In the paper participants were originally classified as shown in the table below in the columns labeled “Original version,” but should have been classified as shown in the column labeled “Corrected version.” The consequence of this misclassification is a slight overestimation of the prevalence of FH (probable and definite combined), which was originally reported to be 1:137, but in the corrected version is 1:223. Importantly, however, this does not change the main conclusion of the paper, that is, “the prevalence of FH appears to be higher than commonly perceived.” Likewise important, the distribution of FH by age and gender (Figure 1) and the risk of coronary artery disease (CAD) by FH (Figure 2) were similar to those originally reported. The authors sincerely apologize for this error.

doi: 10.1210/jc.2014-3926

So after the caption in the Authoritative report, they wrote again, one year later in this Corrigendum: “The consequence of this misclassification is a slight overestimation” and that “this doesn’t change the main conclusion of the paper.” And it’s true, the “conclusion” is still inflated with false positives. “Missclassification” sounds as if it were as simple as hitting the wrong key on a keyboard, but the error had been with the execution of the methodology, a sustained effort, not with data entry in a final draft of a report. This is not insubstantial. It is the difference between the momentary act of reporting and the sustained and purposeful act of building.” One could expect a casual slip with the former, not with the latter.

On the right, I’ve put together a table representing the different mathematical outcomes to the different prevalence rates: (1) the standard minimum of 1:500 estimated by a Nobel Prize winner, (2) the Authors’ corrected 1:223, and (3) the 1st reports’ use of the nonstandard cutoff of 5: 1:137. These differences are not “slight.” The denominator 223 is 63% higher than 137, and nonetheless still doubles the established prevalence estimate of FH.

And what was the reason for lowering the clinical floor of the “Probable” category? Why one number and not the other? If one lowers the standard, wouldn’t one take it for granted that there will be more errors? ... more false positives in the result? Where is the accounting for this? In shifting from 6 to
5 did the study find new mutation carriers or simply increase the error rate beyond acceptability? But then even after making this “correction” don’t we still have the same problem? Without a concern for false positives does the mere exercise of blending the lower category in with the highest actually find more mutation carriers or have we simply inflated the result with a disproportionate number of errors? If 5 wasn’t acceptable, why settle for the nonetheless low standard of 6 and not 8 or 9? By definition, lowering a standard for accuracy increases errors.

Genetic Identification

If I pull in a few overlooked patients by lowering standards...

... I necessarily pull in even more errors.

+ +

Looks like there is a mutation and there is.

- -

Looks like there is a mutation but there is not.

Lower Clinical Detection Point

Looks like there is a mutation but there is not.

Does not look like there is a mutation and there is not.

Does not look like there is a mutation but there is not.

➢ Summary: Stepping backwards to view a tomato from 20 yards does not make it a red apple. Likewise, lowering standards for diagnosis does not increase a patient population. It inflates the count with false positives.
A similar prevalence tactic: Injecting a sliver of inflated results

The Regeneron report added in a group from a catheterization laboratory. This was disclosed, along with a partial disclosure of resulting distortions through “Ascertainment Bias,” which is a form of selection bias. In brief, it is only natural that a population of patients already selected for clinical treatment will tend to have a higher prevalence of illnesses. And if that clinic is related to cardiovascular problems, then naturally it will have a higher concentration of those with the underlying causes of the problem, including FH. Sure enough, when the 6,747 from the cardiac catheterization laboratory were excluded, the prevalence of FH among the less selected population became 1:256. When isolated, the FH patients from the lab had a prevalence of 1:118. This small group, only 13% of the 50,726, accounts for the distortion of the final result, from 1:256 to 1:222.

One problem with the disclosure is that it is not complete. We know that the 6,747 lab patients accounted for 57 of the mutation hits in the overall study. But we don’t know how these are broken down. For example, how many are LDLR and how many are APOB? And how many of the APOB are p.Arg3558Cys?

This is important because p.Arg3558Cys are included in the 50,726 in spite of their controversy: they are milder and some scientists have declared that despite laboratory findings (in vitro) they are not strong enough in living subjects (in vivo) to be considered to have hypercholesterolemia. (See page 129.)

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\(^{21}\) As noted by the authors, other distortions from selection bias still remain after the removal of the 6,747. However, the most notable instances are the inclusion of the Amish of Lancaster, PA and the exclusion of non-whites.
Also, even the standard APOB mutations are weaker than LDLR, as can be seen in the screenshot on the right taken from the 2nd report. The results in the table on the right are from a random selection of an unselected population, and are then later subjected to the selection bias of a clinical scoring system. We don’t expect the LDLR-APOB proportions to match up with the above Regeneron selection biased result in the 6,747. We use them here only to illustrate the principle that the APOB are milder, and will probably result in fewer carriers in a clinical setting than the much stronger LDLR mutations. From this, it is not beyond reason to estimate a disproportionate loss of LDLR verses the APOB when the mutation-rich population of 6,747 is eliminated. Or, another way of saying this is that there were probably fewer APOB among the 6,747 patients in the lab to begin with, and in fact, there would be very few, if not a complete absence of the very mild p.Arg3558Cys, in vivo.

And so when we subtract the inflated 6,747 from the 50,726 we also subtract more LDLR than APOB. Thus, it is probable that among the less selected 43,979 remaining, an even greater disproportion of APOB over LDLR would remain. It is widely known that in the general population APOB is rarer than LDLR. This can be flipped however if one concentrates solely on whites of European descent, then adds in a sliver of those with Founder Effect (the Amish of Lancaster, PA), and also skips over the controversy surrounding p.Arg3558Cys, including them.

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22 See page 116 for a list of reports.
23 This assumes the Amish were not overrepresented in the 6,747.
24 See also page 18 for another explanation of the mathematical consequences of reversing a selection bias.
Goosing denominators before calculation

In the 2nd Danish report, “Patients” are mathematically derived by inflating key denominators before calculation.

**Analogy** (Skip to page 42 to dive right into the material. For a more gradual approach please begin here.)

The authors goosed the denominator of a key metric, lowering the fraction, which, after division, inflates the outcome. This could appear complicated (at first), so we will use a simple analogy that shares the same mathematical structure. Imagine that a school administrator is evaluating a 4H class which is tending animals. He has some numbers, but he will have to derive the others.

Crucially, he knows that each student has the same animals and in the same proportion as the other students.

The administrator is asked to answer the questions:
1. How many total living things are in the whole class?
2. How many total mammals are there?
3. How many birds?

He is given enough in the above table to carry the known proportion of each student over to the entire class.

**How many living things are in the whole class?**

Using the sample student’s numbers, he knows that the proportion of Geese, Cows, Sheep, and Pigs to total Living Things is 6 \( \div \) 12, or .5. Turning his attention to the whole class, he sees 60 such Geese, Cows, Sheep and Pigs. With an eye on the established proportion of 50%, he can divide 60 by .5 and end with 120 total living things.
How many mammals?

He knows that for one student the proportion of Cows, Sheep, and Pigs to total Mammals is 4:10, or .4. The class has 40 such Cows, Sheep and Pigs, so he can divide 40 by .4 and end with 100 total Mammals. Subtracting 40 from 100, he calculates 60 “other mammals.”

Essentially, what he is after when he calculates the fraction 4/10th is, “How many other mammals are there? Dividing the known mammals by 4/10th will give us the total number of mammals, and from that we can derive through subtraction the number for the “Other mammals.”

<table>
<thead>
<tr>
<th>Living Things</th>
<th>Sample Student</th>
<th>Class of 10 students</th>
</tr>
</thead>
<tbody>
<tr>
<td>geese</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>cows</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>sheep</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>pigs</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Other mammals</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Other birds</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Mammals</strong></td>
<td><strong>10</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Birds</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td><strong>Total Living Things</strong></td>
<td><strong>12</strong></td>
<td><strong>120</strong></td>
</tr>
</tbody>
</table>

**Important note to be kept in mind for later chapters:** this methodology depends upon symmetry of proportion between the sample student and the class of 10 students. Without a sufficient degree of symmetry, the methodology fails. For example, if the sample student has 2 cows, but the actual class of 10 students has 30 cows, and not the 20 required by symmetry, then the result will be skewed. We will derive our 50% proportion from the sample student, but then after carrying this proportion over to the whole class, instead of dividing 60 by .5, we will divide 70 by .5. With mammals and birds combined at the outset, we calculate \(140\) instead of 120.

Additionally, good math is reversible, these numbers would not be. Let’s call this \(140\) our “top-down” total.

Without symmetry, if I first separate the birds from the mammals, I reach a “bottom-up” total of \(145\) animals.

- Birds: \(20 \div 1 = 20\)
- Mammals: \(50 \div .4 = 125\)

If I reverse the “top-down” total of 140, by the established 50% proportion, I end with 70. With the “bottom-up” total of 145, I end with 72.5

Presuming a symmetry that does not exist, the math leaks. The results are unreliable.

How many birds?

He does the same for the birds. There are 2 geese. There are no other birds to speak of. Thus, there is no “fraction” of geese-to-total-birds to calculate or work with. Since we had a step where the mammals were divided by .4, as a formality we might also divide the number of geese by 1, but otherwise it is a meaningless exercise: \(20 \div 1 = 20\).
Error

What if I first conflate the word, “geese,” with the ambiguity in the word, “animals,” and then pass them all off as “mammals”? I can now use the total of the whole group (which includes the birds) for my denominator. So instead of deriving a proportion of mammals where Cows, Sheep, and Pigs are divided by 10 Mammals, they are divided by 12 “Animals.” Below, we will put the correct math on the left side of the table and the goosed math on the right. Note how the denominator on the right is inflated due to the inclusion of the geese in total animals, increasing it to 12.

<table>
<thead>
<tr>
<th></th>
<th>Correct Math</th>
<th>Goosed Math</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Student</strong></td>
<td>4 cows, sheep, and pigs ÷ 10 total mammals = .4</td>
<td>4 cows, sheep, and pigs ÷ 12 total animals (mammals + birds) = .333</td>
</tr>
<tr>
<td><strong>Class of 10 Students</strong></td>
<td>Thus, with 40 cows, sheep, and pigs, the proportion demands that I find 100 total mammals in the whole class. 40 ÷ .4 = 100.</td>
<td>Thus, with 40 cows, sheep, and pigs, the proportion demands that I find 120 total mammals in the whole class. 40 ÷ .333 = 120.</td>
</tr>
</tbody>
</table>

How many mammals if I goose the denominator? I get 20 more mammals on paper than actually exist in the barns. I goosed the denominator by counting the named mammals for the numerator, but taking advantage of the ambiguity of the word “Animal” I include the geese in the denominator. This leverages the outcome. And how many birds will I have if I put a pig in the denominator? ... or if I put all the other mammals in the denominator? Why not?

<table>
<thead>
<tr>
<th></th>
<th>Correct Math</th>
<th>Goosed Math</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Student</strong></td>
<td>2 geese ÷ 2 total birds = 1</td>
<td>2 geese ÷ 12 total animals (birds + mammals) = .167</td>
</tr>
<tr>
<td><strong>Class of 10 Students</strong></td>
<td>Thus, with 20 geese for the entire class, and this being the entire population of birds, there is no fraction to speak of. Our divisor is one. 20 ÷ 1 = 20.</td>
<td>Thus, with 20 geese for the entire class, the proportion demands that I find 120 total birds. 20 ÷ .167 = 120.</td>
</tr>
</tbody>
</table>
Again, essentially, what we are after when we calculate the fraction to be used for division is, *How many other birds are there?* The division by the fraction will get us the total number of birds, from that we can derive the missing number. But here, we don’t have a right to the question, because we already have all the birds from the beginning. There are no others. For example, if I say, “*Here is 1/4* of a pie;” and then ask, “*Now what am I missing?*” 1 minus 1/4 = I’m missing 3/4. But if I say, “*Here is a whole pie,“ and then ask, “*What am I missing?*” The answer is, “*Nothing.*” There is no remainder or missing slice: we already have the whole pie.

We get 100 more geese on paper than exist in the barns. *And we can include them under the ambiguous term, “animals.”*

- In all, goosing each denominator while calculating mammals and birds separately, we can *double* the population of animals from 120 to 240, without having to find any new animals in the real world.
Goosing FH with FDB

The four most frequent mutations used in the 2nd report are broken down into the two diseases: three belong to FH and one to FDB. Although FDB APOB and FH LDLR are distinct diseases, the proportion of the top three most frequent FH mutations was estimated after including FDB in the denominator, thus “goosing” the mathematical outcome. Below, here are calculations of LDLR with and without APOB added into the denominators – see the next page for screenshots of raw data.

<table>
<thead>
<tr>
<th>ADH constituent</th>
<th>Proband Found</th>
<th>Total Probands</th>
<th>Consequent Fraction of Spectrum</th>
<th>Total Top3 LDLR</th>
<th>Derived total</th>
<th>Prevalence wf Pop. of 98000</th>
<th>Prevalence wf Pop. of 98098</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR with APOB added</td>
<td>36</td>
<td>142</td>
<td>0.253521</td>
<td>63</td>
<td>248.5</td>
<td>1:394</td>
<td>1:395</td>
</tr>
<tr>
<td>(2nd report)</td>
<td>36</td>
<td>123</td>
<td>0.292683</td>
<td>63</td>
<td>215.25</td>
<td>1:455</td>
<td>1:456</td>
</tr>
</tbody>
</table>

By adding the 19 APOB into the denominator, we inflate the outcome for LDLR. Compare that to the 4H analogy, where we add in the geese to inflate the number of mammals.

**Goosed**

**Added APOB/birds into the denominator for LDLR/Mammals.**

- **LDLR detected in 98,098 Danish**
  - Calculation: \( \frac{36+142}{63} = \frac{2535}{248.5} \)
  - Total LDLR among 98,098 Danish: 248.5

**Goosed**

**Sample Student**

- **geese**: 2
  - Calculation: \( 40 \times \frac{2}{12} = 33.33 \)
  - Total Mammals in class: 120

- **cows**: 2
  - Calculation: \( 40 \times \frac{2}{12} = 33.33 \)
  - Total Mammals in class: 120

- **sheep**: 1
  - Calculation: \( 40 \times \frac{1}{12} = 3.33 \)
  - Total Mammals in class: 120

- **pigs**: 1
  - Calculation: \( 40 \times \frac{1}{12} = 3.33 \)
  - Total Mammals in class: 120

- **Other mammals**: 6
  - Calculation: \( 40 \times \frac{6}{12} = 20 \)
  - Total Mammals in class: 120

- **Other birds**: 0

**Did not subtract APOB/birds. Used total spectrum/animals for denominator.**

<table>
<thead>
<tr>
<th>APOB, R3500Q/W</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR, W66G</td>
<td>21</td>
</tr>
<tr>
<td>LDLR, W23X</td>
<td>13</td>
</tr>
<tr>
<td>LDLR, W556S</td>
<td>2</td>
</tr>
<tr>
<td>Other LDLR</td>
<td>87</td>
</tr>
<tr>
<td>Other APOB</td>
<td>0</td>
</tr>
<tr>
<td>Total APOB</td>
<td>19</td>
</tr>
<tr>
<td>Total Spectrum</td>
<td>142</td>
</tr>
</tbody>
</table>
2nd report’s Supplement, Tables 2 and 3: Goosing FH LDL with FDB APOB

Supplementary Table 2. Characteristics and genetic diagnosis of probands referred for genetic testing for familial hypercholesterolemia.

<table>
<thead>
<tr>
<th>Inclusion period</th>
<th>Referral criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Region of Denmark</td>
<td>2007-2014</td>
</tr>
<tr>
<td>Western Denmark</td>
<td>LDL cholesterol &lt;5.0 mmol/L</td>
</tr>
<tr>
<td>Southern Denmark</td>
<td>if age &lt;16 years and</td>
</tr>
<tr>
<td></td>
<td>one of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>1) Tendon xanthomas in</td>
</tr>
<tr>
<td></td>
<td>first degree relative.</td>
</tr>
<tr>
<td></td>
<td>2) First degree relative</td>
</tr>
<tr>
<td></td>
<td>cholesterol &gt;5.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>adult or &gt;4.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>&lt;16 years.</td>
</tr>
</tbody>
</table>

Supplementary Table 3. Participants in the Copenhagen General Population Study by carrier status of low-density lipoprotein receptor (LDLR) and apolipoprotein B gene (APOB) mutations.

<table>
<thead>
<tr>
<th>LDLR mutation</th>
<th>APOB mutation</th>
<th>Non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=63)</td>
<td>(n=111)</td>
<td>(n=97,924)</td>
</tr>
<tr>
<td>3) Tendon xanthoma.</td>
<td>3) Tendon xanthoma.</td>
<td></td>
</tr>
<tr>
<td>19 inflates the denominator</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screenshot: I’ve added the pointers and emphases.
Goosing FDB with FH

Just as we saw with goosing the number of birds, we shall see that the FDB prevalence leverage is extreme. With inflation, the prevalence is 1:118. Without inflation, the prevalence is 1:884. This is because there is no “proportion” of a spectrum to speak of, since the R3500Q/W make up the whole of the FDB spectrum found in the studies. Below, following the same procedure, here are calculations of APOB with and without LDLR added into the denominators – see the next page for screenshots of raw data.

<table>
<thead>
<tr>
<th>Isolated ADH constituent</th>
<th>Total Probands</th>
<th>Consequent Fraction of Spectrum</th>
<th>Total found</th>
<th>Prevalence wf Pop. of 98000</th>
<th>Prevalence wf Pop. of 98098</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB with LDLR added</td>
<td>19</td>
<td>142</td>
<td>111</td>
<td>830</td>
<td>118</td>
</tr>
<tr>
<td>(2nd report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOB without LDLR</td>
<td>19</td>
<td>19</td>
<td>1</td>
<td>111</td>
<td>883</td>
</tr>
</tbody>
</table>

In the table below, on the left we correctly isolate APOB to calculate APOB; on the right, we put LDLR in the denominator.

<table>
<thead>
<tr>
<th>Correct</th>
<th>Total Detected in 98,098 Danish</th>
<th>Calculation</th>
<th>Total APOB among 98,098 Danish</th>
<th>Total APOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500Q/W LDLR, W66G</td>
<td>19</td>
<td>111</td>
<td>19÷19=1</td>
<td>19÷142=.1338</td>
</tr>
<tr>
<td>LDLR, W23X</td>
<td>21</td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>LDLR, W556S</td>
<td>13</td>
<td>There are no other APOB.</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Other LDLR</td>
<td>87</td>
<td></td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>Other APOB</td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total APOB</td>
<td>19</td>
<td></td>
<td></td>
<td>19÷142=.1338</td>
</tr>
<tr>
<td>Total Spectrum</td>
<td>142</td>
<td></td>
<td></td>
<td>142</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Goosed</th>
<th>Total Detected in 98,098 Danish</th>
<th>Calculation</th>
<th>Total APOB among 98,098 Danish</th>
<th>Total APOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500Q/W LDLR, W66G</td>
<td>19</td>
<td>111</td>
<td>19÷19=1</td>
<td>19÷142=.1338</td>
</tr>
<tr>
<td>LDLR, W23X</td>
<td>21</td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>LDLR, W556S</td>
<td>13</td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Other LDLR</td>
<td>87</td>
<td></td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>Other APOB</td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total APOB</td>
<td>19</td>
<td></td>
<td></td>
<td>19÷142=.1338</td>
</tr>
<tr>
<td>Total Spectrum</td>
<td>142</td>
<td></td>
<td></td>
<td>142</td>
</tr>
</tbody>
</table>

When we calculate the fraction of the spectrum, we are really asking, How many other APOB are there? And we don’t have a right to the question, because we already have all the APOB from the beginning. There are no others. 19 is not half of an amulet, from which we can derive another half. 19 is the whole amulet: 19 probands ÷ the proband total of 19 = 1. And so 111 APOB molecular hits in the Copenhagen sample ÷ 1 = 111 APOB total mutation carriers in the Copenhagen sample.
2nd report: Supplementary Goosed FDB APOB Denominator

Supplementary Table 2. Characteristics and genetic diagnosis of probands referred for genetic testing for familial hypercholesterolemia.

<table>
<thead>
<tr>
<th>Inclusion period</th>
<th>Capital Region of Denmark Tybjerg Hansen</th>
<th>Western Denmark Damgaard et al.1(1)</th>
<th>Southern Denmark Brugger et al.1(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral criteria</td>
<td>LDL cholesterol &gt; 5.0 mmol/L or &gt; 4.0 mmol/L if age &lt; 16 years</td>
<td>At least one of the following criteria: 1) Tendon xanthoma in patient or first degree relative. 2) First degree relative with LDL cholesterol &gt; 5.0 mmol/L in an adult or &gt; 4.0 mmol/L in a child &lt; 16 years. 3) Coronary or vascular disease before age 60 years in first degree relative, or before age 50 years in second degree relative(3)</td>
<td></td>
</tr>
</tbody>
</table>

Supplementary Table 3. Participants in the Copenhagen General Population Study by carrier status of low-density lipoprotein receptor (LDLR) and apolipoprotein B gene (APOB) mutations.

<table>
<thead>
<tr>
<th>LDLR mutation</th>
<th>APOB mutation</th>
<th>Non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=63</td>
<td>n=111</td>
<td>n=97,924</td>
</tr>
</tbody>
</table>

- **LDLR**
  - n=63
  - 19 LDLR
  - 21 LDLR
  - 13 LDLR
  - 2 LDLR
  - 80 LDLR
  - 7 LDLR
  - 0 LDLR
- **APOB**
  - n=111
  - 19 APOB
  - 19 APOB
  - 17 APOB
  - 3 APOB
  - 80 APOB
  - 3 APOB
  - 0 APOB
- **Non-carriers**
  - n=97,924
  - 111
  - 111
  - 98,098

**Notes**
- LDLR included in total (denominator) when calculating for APOB.
- The remainder of the spectrum are all LDLR. We know of no significant “remainder” for APOB spectrum. R3500Q & W are the given spectrum.
- 123 inflates the denominator within APOB
- 19 APOB + 123 LDLR = 142
Background review of 2nd report’s total prevalence: FH + FDB

Let’s review how the 2nd report derived FH prevalence (FH+FDB). 55 probands were found among the Top4 mutations. In total, 142 probands were found in the whole spectrum. (This means that there were 87 probands found within the spectrum that were not in the Top4. I call these the “Ex-Top4” probands.) Thus, the 55 Top4 probands are 38.7% of all probands found. (55/142=.387).

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Probands in spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500Q/W</td>
<td>19</td>
</tr>
<tr>
<td>LDLR, W66G</td>
<td>21</td>
</tr>
<tr>
<td>LDLR, W23X</td>
<td>13</td>
</tr>
<tr>
<td>LDLR, W556S</td>
<td>2</td>
</tr>
<tr>
<td>Other LDLR</td>
<td>87</td>
</tr>
<tr>
<td>Total Spectrum</td>
<td>142</td>
</tr>
</tbody>
</table>

ADH Prevalence: FH LDLR & APOB combined.

<table>
<thead>
<tr>
<th>LDLR &amp; APOB detected in 98,098 Danish</th>
<th>Calculation</th>
<th>Total among 98,098 Danish</th>
</tr>
</thead>
<tbody>
<tr>
<td>174</td>
<td>55/142=.387</td>
<td>450</td>
</tr>
<tr>
<td></td>
<td>174/.387=450</td>
<td></td>
</tr>
</tbody>
</table>

98,098 ÷450 = 2.17 .9956

In the general population, it was too expensive and time consuming to test everyone for all known mutations and so only these four most frequent mutations were targeted. This is the reason why we are carrying the ratio of Top4-to-total probands in the spectrum over to the Top4 hits in the general population. We want to use this ratio to factor the Ex-Top4 into the Copenhagen study’s molecular results, giving us “FH” prevalence (“FH” = FH+FDB).

In this parallel set of numbers, a total of 174 Top4 mutation carriers were found in the Copenhagen study. How many hits would we have if we had included the Ex-Top4 mutation carriers as targets? We divide 174 by the .387 to factor in the remainder of the mutation carriers in the population and arrive at total of 449.6, which we will round up in the

25 Review of report relationships: The Authoritative report depends entirely upon the 1st report and its corrigendum. The 2nd report shares 60,000 of its population with the 1st report. The 2nd report declares that its results are comparable to those of the 1st report.

26 Red Flag: Compared to the 2nd report’s use of Tybjærg-Hansen’s results, Brusgaard’s much larger spectrum list determined a different set of four most frequent mutations for Denmark. And even when considering the same Top4 mutations used for the 2nd report, his data suggests a 50% proportion to the rest of the spectrum, not 38.7%. That would lower the prevalence results. See Brusgaard, et al, and Supplement to the 2nd report.
authors’ favor to 450. Dividing the population of 98,098 by 450 we arrive at 1.217.9956. We must round down against the rules to get the 217 found in the report. (There is another red flag here; see footnote 27.)

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27 Red Flag: Although the title to the report uses 98,098, the actual constituents of the population were not rounded and they totaled exactly 98,000. Elsewhere, 99,098 is used. And the math supporting some of these numbers simply does not add up. For details and screenshots, see pages 105 and 106.
The traditional number for HeFH prevalence is 1:500. So how is it that these new prevalence numbers are so different?

First, 111 of the 174 mutation carriers found were FDB. Only 63 were FH. So FDB was conflated with FH. That’s a linguistic event, not a recognition of new patients.\(^{28}\)

When the authors separate the FH and FDB numbers, what do we find?

\(^{28}\) See page 14.
Good math is reversible; these numbers are not.

As we said earlier, the methodology requires symmetry of proportion between the spectrum and the general population. Without that, the results will be unstable. And the results below are indeed unstable. Add this instability to the inflation of key denominators, and the problem is even more conspicuous. When the report teases out the FH and FDB and calculates them individually “from scratch,” the numbers are not consistent with the report’s total when FH and FDB are combined at the outset of calculation. We can see this clearly by looking at the study’s results. If the prevalence of FH LDLR + FDB APOB is supposed to be 1:217, then out of a population of 1,000,000 we would expect to find 4,608 mutation carriers. But if we accept the breakdown then the LDLR portion of 1:395 gives us 2,532 out of 1,000,000 and the APOB portion coming in at a rate of 1 for every 118 gives us 8,475. Adding the two constituents together we get 11,007, which yields a prevalence rate of 1:91, next to the 1:217 prevalence rate found in the results, which gave us 4,608 ... so which is it?

The predominance of LDLR over APOB probands in the spectrum actually inverts and suddenly APOB is more prevalent than the LDLR hits in the 98,000 sample. This is obvious when comparing the study’s population results to the spectrum probands used to derive the ratio. (It is also obvious when comparing the results to the probands in Brusgaard’s paper.)

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29 See page 39.
Note that, in the results (above left), the reports’ FDB APOB prevalence rate of 1:118 is higher than the FH LDLR rate of 1:395. Again, per million, the FDB APOB’s 1:118 yields 8,475 mutation carriers and the FH LDLR’s 1:395 yields 2,532. This is upside down. It is well established in the industry that the LDLR mutations, as a whole, are more prevalent than the disease-causing APOB mutations. And the authors have already shown in the 2nd report Supplement that APOB R3500Q/W make up only 13% of the total probands found (FH LDLR + FDB APOB) (above right). But then, as we see, in the results, APOB mutations suddenly outnumber the LDLR by over 200%.

For their ADH (FH + FDB) prevalence, the whole business of carrying over the .387 fraction of Top4 probands rests on the unstated assumption that there is a symmetry of proportion between the spectrum and the Copenhagen sample population. We can only expect a roughly accurate result if the proportions between the two sets of numbers are roughly parallel.
Although inflating the denominator accounts for much of the distortion, even before this, we can see the inversion in the raw data. In the 2nd report’s Supplementary, Table 2, we see the number of FDB APOB to FH LDLR is 19 APOB for 36 Top3 LDLR in the spectrum, but this predominance of LDLR flips when the report presents the molecular hits from the 98,000 Copenhagen residents. We now have 111 APOB for 63 Top3 LDLR. There were almost twice as many Top3 LDLR as APOB in the spectrum, but then when we get to the molecular hits in the population study, we see the opposite: the Top3 LDLR are outnumbered by twice as many APOB. This is a view of the raw data before denominators were inflated, so we have more than one problem with this inversion of LDLR predominance.

The assumed symmetry of proportion between the authors’ reported spectrum and their reported population is just not there. But we can’t yet disagree on the size of the gap between estimates. First, we must deal with the outright reversal in the established predominance of LDLR over APOB … just as we wouldn’t disagree about the difference between the size of an elephant compared to that of a mouse until we first confronted the suspicious statement that the mouse was bigger than the elephant. Such a reversal in FH predominance over FDB might apply to a geographical region subject to founder effect, but I have found no expert opinion stating that FDB prevalence outnumbers FH prevalence in a sufficiently diverse population. It is universally agreed that FDB is the rarer of the two.

The 2nd report, Table 1, contradicts established prevalence ratios of FDB to FH, which are roughly 2 for every 1. The raw data here shows 111 FDB (APOB) for 63 TOP3 FH (LDLR), a predominance of APOB over the Top3, and possibly an equivalence of total FH (LDLR) to total FDB (APOB) in the general population. It is curious that if this reversal or even parity between the two classes of mutations is correct, then it would have been a brilliant discovery. Why didn’t the authors lead in with this story?

We can at least say one thing with confidence: the method of using a proportion of probands in the spectrum to calculate prevalence in the general population is unstable. We should have seen this coming. A proband to members of a family is like a hub to the spokes of the wheel. Different wheels have different ratios of spokes to hubs, and different cultures within a single nation have different family sizes. Can I really assess a portion of hubs relative to total hubs in a small town and then use this proportion on a fraction of spokes in a large city in order to tally up all spokes in that city?

How to accurately determine that ratio is worthy of further debate. Since, however, we are reconciling the authors’ own reports, we will later continue to use their .387 fraction. Readers are invited to substitute their own
estimates in the equations. Even a wide range of estimates will show that the larger problem is with the method used and not just the ratio chosen. For example, suppose that I ask, "What is the ratio of black to white pearls?"... while referring to a necklace which includes white plastic beads. There may be this or that proposed ratio, which needs to be resolved. But the bigger problem is the existence of plastic beads where one expected pearls. Likewise, the issue of the ratio of Top4 mutation carriers to Ex-Top4 needs to be resolved. But we mustn’t take our eyes off of the bigger issue: False Positives are included in results where one expected genuine mutation carriers. We will demonstrate this swap later in the core deduction, beginning on page 62. Keeping this in mind for later, let’s continue our evaluation of the leveraged denominators.

FH LDLR and FDB APOB prevalence, without leveraging the denominator

Let’s return to the leveraged denominator, and see what numbers we come up with if we hold to correct mathematics. If we treat each disease separately, we see that of the 55 Top4 probands in the spectrum 36 were FH and 19 were FDB.\(^{30}\) We see that the 19 FDB probands in the spectrum and the 111 FDB mutation hits in the general population had only R3500Q and R3500W mutations. Practically speaking, these two mutations constitute the total spectrum for FDB. Other mutations are extremely rare. Here are three of the same authors in the Authoritative report. (R3500Q = Arg3500Gln\(^{31}\))

\(^{30}\) See page 122, “2nd report, Supplementary.”

http://ltd.aruplab.com/Tests/Pub/0055654.
http://cardiovascmed.com/?page=article&article_id=29134
And here are two of the same authors again. (R3500Q = Arg3500Gln)

In conclusion, our results suggest that the Arg3500Gln mutation is at present the only known APOB mutation worth screening for in white patients with hypercholesterolemia or ischemic heart disease and their relatives.

In the studies used in the 2nd report, no other mutations were included in the FDB APOB spectrum. We have the whole pie, and so there is no missing slice to calculate. As an exercise, however, we would remain consistent by filling out the equation: 19 probands found ÷ a total of 19 probands in the whole FDB APOB spectrum = 1.32 Now there were 111 FDB APOB found in the general population. So we divide 111 by 1 and arrive at total of 111 FDB APOB. Again, we do not have to account for a remainder. There is nothing like an “Ex-Top4” when it comes to FDB APOB. All Ex-Top4 belong to the FH LDLR spectrum. So from the population of 98,000 we divide by the 111 FDB APOB found, and our FDB prevalence is 1:883.33

Correct

<table>
<thead>
<tr>
<th>Probands in spectrum</th>
<th>APOB detected in 98,000 Danish</th>
<th>Calculation</th>
<th>Total APOB among 98,000 Danish</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500Q/W LDLR, W666G LDLR, W23X LDLR, W556S Other LDLR Other APOB</td>
<td>19</td>
<td>111×19=1 111×1=111</td>
<td>111</td>
</tr>
<tr>
<td>Total APOB</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correct

<table>
<thead>
<tr>
<th>Sample</th>
<th>Calculation</th>
<th>Total Birds in class</th>
</tr>
</thead>
<tbody>
<tr>
<td>geese</td>
<td>2×2=1=20÷20=2</td>
<td>20</td>
</tr>
<tr>
<td>cows</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>sheep</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>pigs</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other mammals</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Other birds</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total Birds</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total Animals</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

There are no other APOB/Birds.

32 In the 2nd report, it is unclear whether the authors lumped R3500Q with R3500W together or not. Supplementary Table 2 suggests that they did. Table 3 suggests that they did not. However, the difference would be negligible. One of the supporting sources for the 2nd report, Brusgaard, listed 2 mutation types for APOB, where R3500Q proband hits to R3500W proband hits were 40 to 1, and where only 1 R3500W mutation was found. If the authors’ only targeted R3500Q, then when factoring in the remainder of the spectrum the number used for division would be: 40÷41=.976. The difference in results would be negligible. Total results (IE, not distilled into probands) were 75 hits for R3500Q, and only 1 hit for R3500W, that’s 75 R3500Q of a total 76 APOB mutations found. No other harmful APOB mutations were found besides these two.

33 The disagreement between my 1:883 and the authors 1:884 is due to the population discrepancy between 98,000 and 98,098. See pages 105 and 106 for more on this red flag.
This leaves us with the FH LDLR spectrum. Specifically referring to Denmark and the molecular results in Brusgaard’s study, 53 different LDLR mutations were found.\textsuperscript{34} Because there are more LDLR mutations in the spectrum besides the three most frequent, we will calculate the remaining proportion of the spectrum. But we will subtract the FDB APOB probands from the total probands because we are only calculating a ratio for FH LDLR.\textsuperscript{35} So \( \frac{36 \text{ probands}}{123 \text{ total probands in the LDLR spectrum (not 142) }} = .2927 \). That gives us a total of 215 in the general population, representing the 63 carrier of the three most frequent mutations plus the remaining 152 carriers of the other LDLR mutations ((63 ÷ .2927 = 215 total and 215 – 63 = 152)).\textsuperscript{36}

<table>
<thead>
<tr>
<th>Correct</th>
<th>Probands in spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500Q/W</td>
<td>19</td>
</tr>
<tr>
<td>LDLR, W66G</td>
<td>21</td>
</tr>
<tr>
<td>LDLR, W23X</td>
<td>13</td>
</tr>
<tr>
<td>LDLR, W556S</td>
<td>2</td>
</tr>
<tr>
<td>Other LDLR</td>
<td>87</td>
</tr>
<tr>
<td>Other APOB</td>
<td>0</td>
</tr>
<tr>
<td>Total APOB</td>
<td>19</td>
</tr>
<tr>
<td>Total Spectrum</td>
<td>142</td>
</tr>
</tbody>
</table>

We are calculating for LDLR/Mammals, so we do not include APOB/Birds

Without leveraging the denominators prevalence approaches established rates.

In the table on the right, we can see that across the board the prevalence numbers are significantly higher for the leveraged denominators. In the middle column, we calculate with the unleveraged denominators, while otherwise using the reports’ own sets of numbers. We arrive at very different conclusions. Prevalence, without leveraging the denominator, returns to estimates established by previous scientists. Here are the elements to the full calculation, broken down into the ADH constituents: FH LDLR and FDB APOB.

\textsuperscript{34} The text in Brusgaard, et al, uses the number 54 as the total of all mutation types found. In Brusgaard’s report, I manually counted 55 on Table 2, 53 of which were LDLR.

\textsuperscript{35} Note that without the FDB here, we are no longer talking about the Top4 as we did before, since we have subtracted out one of the elements from the Top4. We are now working with the three most frequent FH LDLR mutations.

\textsuperscript{36} “Ex-Top4” – See “Terms” on page 121.
The traditional FH LDLR prevalence is 1:500. Using the authors’ own data, I come up with 1:456. That’s only about 10% off. For FDB, the prevalence is held by established scientists to be 1:1000. The authors’ numbers, without inflating the denominator, come in at 1:883. With leveraging, it is 1:118.

**No Symmetry of proportion**

Note that these corrected numbers are not reversible either. “Top-down” and “bottom-up” calculations do not match up. Beginning with the total 174 and dividing by .387, I end with a prevalence of 218. However, breaking down my calculations into FH and FDB separately, adjusting the ratio accordingly, I end with a prevalence of 301. This is more evidence of asymmetry. (See pages 39 and 51.) A symmetry of proportion between the spectrum and the results in the general population just does not exist. No one’s math is leakproof with the information provided.

**Without “Cherry-picking,” the numbers return to estimates established by previous scientists**

Cherry-picking the most aggressive of three presented ratios, gooses the key denominator before calculation. The Authors’ and other scientists’ data presented in this selfsame report, averaged, return prevalence to normal.

To calculate the prevalence of 1:217, the authors’ blended both FH and FDB and then used a divisor of .387 to calculate in the remainder of the spectrum. But in their report they also included spectrum detail from two other science teams, Damgaard, et al, and Brusgaard, et al. If we wish to avoid cherry-picking, we should average all three results. Also, if we want to calculate FH LDLR alone, to avoid conflating FH and FDB, then we take out FDB. Now our average divisor is .3362.

<table>
<thead>
<tr>
<th>Author (numerator/denominator)</th>
<th>Tybjær-Hansen (36/123)</th>
<th>Damgaard (39/119)</th>
<th>Brusgaard (73/188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top3 LDLR fraction of spectrum</td>
<td>0.2927</td>
<td>0.3277</td>
<td>0.3883</td>
</tr>
<tr>
<td>Avg. Top3 LDLR fraction of spectrum</td>
<td>0.3362</td>
<td>Targeted found 63</td>
<td>Targeted and Untargeted found 187</td>
</tr>
</tbody>
</table>

Cherry-picking the most extreme of the three presented ratios, leverages the denominator before calculation. Without leveraging or linguistic conflation, we return to an FH LDLR prevalence slightly lower than the established 1 in 500.

---

37 2nd Report, Supplementary Table 2.
In the strategy room, swapping patients

Clinical scoring systems for FH, such as the DLCN, are inaccurate. If you tighten up such a system in order to avoid false positives, you leave out a majority of mutation carriers. If you loosen up the criteria to recover a number of previously overlooked mutation carriers, you bring in a disproportionately larger group of false positives. And so when the genetic proof of overlooked patients is only the message, while the recommended diagnosis is still the clinical scoring system, then those genuine mutation carriers in the academic abstract are swapped back out of consideration and real non-mutation carriers are swapped in. It’s as if a real estate developer recommended that a bulldozer operator use a map which was faulty. Now, the developer only needs to look down at his own correct map and say, “See ‘X’ marks the spot. Go!” The operator would pick up his own faulty map and act “independently,” illegally taking down a habitat and creating an empty space profitable to the developer. Likewise, Regeneron and the others fund studies which use a molecular map to show that “underdiagnosis exists!” but recommend the inaccurate map of clinical diagnosis to “get there.”

I have demonstrated this in my analysis. I reconciled two research studies, both written by the same authors, and both using the same 60,710-member population. One study focused on a genetic approach and the other was claimed to be solely a clinical scoring system. Although a similar prevalence total, they were of different populations. There was a swap of different groups when moving from one procedure to the other.

This was not a swap limited to these two papers. Whenever the genetic basis of FH is merely the message, while clinical scoring systems are recommended practice, patients are swapped. This is because the majority of mutation carriers are below clinical detection while the majority that are above clinical detection are not mutation carriers. The former are difficult and expensive to find; the latter, easy and profitable. It’s as if a Galapagos scientist made a special drug and then went out to convince everyone that there is a disease specific to a rare, sea-swimming turtle, while showing them how easy it is to find and inoculate the land-based tortoises.

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38 Because the two Danish studies shared the very same population I was able to work with deduction. The 1st and 2nd reports were complicated by the fact that only the four most frequent mutations were screened for. The 2nd report provides a “methodology” to complete the prevalence estimate. Reconciling these two reports therefore is quite elaborate. See page 62 for the mathematical proof by way of this reconciliation.

39 This was not exactly true. Molecular hits were given clinical scores and thereafter considered clinical results. However, most of the results were due to clinical scoring alone. That is, although the genotypes were demoted to phenotypes, most were solely phenotypes to begin with. In parallel epistemology, this is like saying that although those with forensic DNA matches were demoted and considered equal to those with solely circumstantial evidence, most of the suspects had only circumstantial evidence to begin with.
First step: Exaggerated prevalence “proves” and leverages the urgency of “Underdiagnosis”

Let’s look again at the observation by Dr. Adriane Fugh-Berman, expert witness in the Wyeth trial. She was quoted in a Science magazine article regarding deceptive scientific publications:

“People tend to think of marketing messages as ‘buy drug A,’ but that’s never the message imbedded in such articles. .... The message may be, disease A is underdiagnosed or far more serious than previously believed ....”

On the right, we see this strategy in the Regeneron-funded report, coincidentally published in the same magazine. Note the rational leverage that “prevalence” has over “underdiagnosis.”

And below, in the industry’s authoritative report: “Severe Underdiagnosis” ... “under treatment” ... “urgent worldwide need” ... “early and aggressive treatment” ... and “extremely high-risk condition.”

On the left is the report regarded as authoritative in the industry. It is even cited by the FDA and within FDA submitted documents. It conducted no prevalence study of its own, and it has no external, contemporary source for its doubled prevalence.

In the Danish report below, sharing an identical population with the report above, prevalence was supposed to have been confirmed genetically. My analysis however proves, with deduction, that upon reconciliation of the respective reports, this later study provides the facts which refute the “1st report” decisively. See my mathematical proof on page 62. I refer to this report below as the “2nd report.”

Key point: Distorted prevalence serves as “proof” of “underdiagnosis.”
Below, we see the pharma-funded efforts to *educate* the medical community and create awareness of the urgency. The industry wide repetition of “vastly underdiagnosed” suggests that either the education strategy has been influential or there is a concerted effort to broadcast a unified message.

https://thefhfoundation.org/get-involved

This pharma-funded report is considered authoritative. It is even cited by the FDA. It conducts no prevalence study and has no external, contemporary source for its doubled FH prevalence estimate. My previous analysis shows that the only published material supporting these numbers, co-authored by Nordsgaard, relies on manipulated data.
Second Step: *Use selection bias*

An FH clinical scoring system, as if sufficient, is an applied selection bias. So ironically, the cause of underdiagnosis is the recommended selection bias: a clinical scoring system such as the Dutch Lipid Clinic Network criteria (“DLCN”). Most FH mutation carriers score below clinical detection. Therefore, underdiagnosis is as certain as the deception that clinical testing can be sufficient to determine FH. On the other hand, clinical testing *includes* non-mutation carriers in high percentages. The gap between these two exclusive groups reveals the mechanical switch that is thrown by Pharma when we move from the alarming genetic message to the actual front-line clinical diagnosis, a selection bias in vivo. These easy-to-find non-mutation carriers and the real mutation carriers are swapped.

Let genetic proof shout a true alarm of a danger that one’s own recommended diagnostic procedure has actually contributed to and then let the fear herd all through the only available exit, that which *guarantees* the persistence of the danger. Genetic testing *proves* “underdiagnosis!” and then the recommended and culturally prevailing clinical scoring system *guarantees* it.
“Don’t eat the Potato Salad”

Here’s an analogy of passing the “baton” from the message to the selection strategy. Imagine there is a doctor who treats food poisoning and his office is just outside a large conference room where attendees are breaking for lunch. On the left side of the room there is a large dish of potato salad, and on the right, there is another large dish of potato salad. It is learned by the doctor that the potato salad on the left is perfectly fine, but the dish on the right has spoiled and those who have ingested that potato salad will certainly have food poisoning. The doctor of course makes a profit in proportion to the number of patients he serves, not to the degree of health he restores or complications he prevents.

He can make two possible announcements, both of which will be true, sort of.

a) “All those who have eaten the potato salad on the right have a high chance of food poisoning. If you’ve eaten the potato salad on the left, however, you shouldn’t be alarmed. It’s OK. I have an office next door and will provide a remedy to those who ate the potato salad on the right. The remedy may be unpleasant and, to be honest, it’s a little risky, but it is better than doing nothing.”

b) “Attention. The potato salad has a strong chance of giving you severe food poisoning. We’ve found samples of dangerous bacteria and this could be very serious. I have an office next door and will provide a remedy, which may be unpleasant but it is better than doing nothing.”

Or to put it differently ….

- Making an **adequate distinction** between those poisoned and those not poisoned is the best **health** strategy. Why subject those who were *not* poisoned to a risky treatment?
- Making an **inadequate distinction** between those vulnerable to the poison and those vulnerable to one’s best financial strategy is, well, the best financial strategy.

If an inadequate clinical scoring system is the inherited cultural assumption and academic studies continue to reinforce that assumption by actually recommending it, while shouting the alarming molecular fact of “Underdiagnosis!” where will all these targets be sent?

- Making an **inadequate distinction** between those vulnerable to FH and those vulnerable to one’s best financial strategy is the best financial strategy.
- Making a **competent distinction** between those with and those without the FH mutation is the best **health** strategy.
Reconciling 1st & 2nd Danish reports: 1 page mathematical proof of the patient swap

If pearls were swapped with plastic beads, the quantity of pearls swapped would be a different issue from the swap itself. Here, we will set aside the issue of quantities and demonstrate the fact of the swap itself.

Summary of the Critical Fracture when reconciling the 1st and 2nd reports (or phenotyped and genotyped FH populations)

The Total results minus Mutation Carriers equals False Positives.

Thus, if the Total alone is reduced, False Positives will also be reduced, mathematically.

Mechanism: identification of one portion of mutation carriers was not physically possible within the 1st report’s methodology. Thus, their exclusion from the Total, while nonetheless calculated within the equation, results in a mathematical reduction of the variable for False Positives, manipulating the perception of accuracy, and as good as renaming those false positives as genuine mutation carriers.

Variables:

FP = False Positives, I.E., erroneous clinical determinations.
the Total = Total results of the 1st report (not FP)
A = Mutation carriers who were originally Above the clinical detection point.
B = Mutation carriers who were originally Below the clinical detection point.
T = The carriers of the most frequent mutations. Only these were targeted in the molecular test.
X = The remaining carriers of mutations. These were not targets and must be derived from T.
R = Reasonable ratio of T to all mutations, or \(\frac{T}{T+X}\).

Assumed:

That the distribution of X within the clinical results will be closer to that of T’s distribution than to the inverse of the distribution of T thus far. (E.G., a majority of T were below clinical detection in the 2nd report.)

Sufficient equation:

1) The Total – Mutation Carriers = False Positives. Therefore, Total – (AT + AX + BT + BX) = FP.
2) We can derive X from T: AX = \(\frac{AT}{R}\) – AT and BX = \(\frac{BT}{R}\) – BT. Therefore: Total – (AT + \(\frac{AT}{R}\) – AT + BT + \(\frac{BT}{R}\) – BT) = FP.
3) Or to say the same thing, Total – (AT + BT + \(\frac{AT}{R}\) – AT – BT) = FP.
4) Since AT + BT make up all of T, this leaves the simplified equations attractive: Total – \([T + \frac{T}{R} – T]\) = FP or Total – \(\frac{T}{R}\) = FP.
5) However, if I thus combined AT and BT before publication and then presented only T to my reader, then it is a responsible equation, if and only if, the presence or absence of BX is accounted for in both the Total and the derivation of X. The Total would only be truly total if \(\frac{T}{R}\) truly accounted for all of X, which necessarily includes BX.
6) If BX is physically excluded from the Total results by the methodology, then any responsible mathematical derivation for X must also exclude BX: Total – (AT + \(\frac{AT}{R}\) – AT + BT) = FP. The simplified equation cannot be used.
7) However, the 1st report excludes BX, real people, through the chosen methodology but does not explain this. There is no “above” or “below” detection for T shown in the finished report, because all molecular hits were assigned – before publication – higher clinical scores by the fact that they were carriers. This may or may not make clinical sense, but academically this is an act of obfuscation: the reader, as a latecomer, most naturally will make no assumption of a BX category and has no information to challenge use of the simplified equation: Total – \(\frac{T}{R}\) = FP.

However, these real people (BX) are actually missing, and so are actually missing from that Total. And as we’ve seen, if the Total alone is reduced, FP will also be reduced, mathematically. All the while, the real-world BX are missing from the Total yet are still derived mathematically through the abstract relation of X to T. Therefore, X as \(\frac{T}{R} – T\) will inflate mathematically to maintain its proportion in relation to the variable, T, thus compensating the absence of the real carriers, here represented by the variable “BX,” with what can only be false positives.

- The “swap” is due to the exclusion of real BX from the results while preserving its mathematical derivation within the equation. This fracture lies within the source for the report regarded as authoritative and which has influenced regulators, insurance carriers, and the medical community: “FH” is downstream redefined patients. Not only are real mutation carriers thus swapped out, but the math has helped justify a diagnostic procedure by which easy-to-find, non-mutation carriers are penciled in for prescriptions, for a genetically inherited disease.
Reconciling 1st & 2nd Danish reports using the maximum & minimum numbers mathematically possible

| T  | X  | FP 
|----|----|----
| A  | ≤25|     |
| B  | ≥75|     |

Total $T = 100$.

Because the 2nd report adds in a new sample to the 1st report’s sample, and because the total AT of both samples is 25, AT in the 1st report’s sample, as a portion of that total, cannot possibly be more than that total of 25. It follows then that because the total of $T$ in the 1st report was 100, AT cannot possibly be less than 75 in the 1st report.

| T  | X  | FP 
|----|----|----
| A  | ≤25| ≤40 |
| B  | ≥75| ≥119|

AX = AT/.387 – AT

≤25/.387 – ≤25 = AX

AX ≤ 40

In the 2nd report, the authors tell us that $T$ is 38.7% of total mutations. However, the ratio itself does not account for the “swap” of genuine mutation carriers for false positives. I invite the reader to try .3, .4, and .5 or some other reasonable estimate. As demonstrated on the preceding page, the “swap” is due to the unmentioned exclusion of BX.

| T  | X  | FP 
|----|----|----
| A  | ≤25| ≤40 |
| B  | ≥75| ≥119|

BX = BT/.387 – BT

≥75/.387 – 75 = BX

BX ≥ 119

However, BX are by definition below clinical detection and so cannot have been flagged clinically. What’s more, BX were not targeted in molecular screening and so cannot have been included in the molecular results. They were abandoned.

| T  | X  | FP 
|----|----|----
| A  | ≤25| ≤40 |
| B  | ≥75| ≥119|

We use a Total of 284 results in the 1st report, after “equalizing” the clinical results to the same scale as the molecular. (Originally 309, which still shows the swap. Not bringing the two results to the same scale works against the authors here.)

284 – ≤25 – ≤40 – ≥75 = FP

FP ≥ 144

If I combine AT and BT, and then apply the ratio of .387, then I necessarily include the ≥119 heretofore thrown away by the diagnostic procedure, but this demands that I also account for the ≥119 in the total. To say it again, these ≥119 could not possibly have been included in the authors’ 284, given their procedure. They are now accounted for here: Total = 403.

Deception

| A+B | T  | X  | FP 
|-----|----|----|----
|     | 100| 159| 25.6|

If however I make no accounting for the ≥119 BX, which had been excluded by the recommended methodology, then I can combine AT and BT before publication of the results, and leave it to the reader to assume the counterpart, using any reasonable ratio to estimate X from T. BX are real people and they are not represented in this equation; X is only mathematically derived, effectively renaming a quantity of FP, while the variable representing FP is itself reduced.

It is only after the 2nd report that we learn that AT could not possibly be more than 25, and from here we can make crisp deductions. BX is the larger of the four groups of mutation carriers and they cannot possibly be in the results. These genuine mutation carriers are also the least profitable of existing patients, where the most profitable false positives only require the acceptance of this procedure. The unmentioned gap in the math has justified a clinical procedure which effectively renames these errors as “True Positives,” without leaving anything for a reader to blink at. The ≥119 real people are abandoned, while in the abstract, false positives fill their void, the published report leaving very real consequences in the diagnostic determination of “FH.”
Reconciliation of the 1st & 2nd Danish Reports, in greater detail

How the authors got the 1:223 in the 1st report, a Corrigendum for the Corrigendum:

The authors blended molecular and clinical results and derived a prevalence rate against a population of 69,016, concluding 1:223. Here we will tease the two constituents apart and then compare each on the same scale. Consequently, we will also be adjusting a key number by 12%.

In review, the 1st Report’s prevalence was actually 1:137. To reach this the authors lowered the clinical cutoff point into the third lower category, off-text, enabling them to blend in a less accurate count. In short, off-text, 5 was actually used as the clinical cutoff point, while on-text they printed “6.” (See page 30.) Their off-text cutoff point may have been called into question, since they later issued a corrigendum and apology. To arrive at their new number, 1:223, they thus took out this slice from the third lower category, yet they still blended in the second lower category.

But there is a little more here. Even the 1:223 involves another form of blending. One key aspect of the 1st report is the mixing of the molecular results in with the clinical results. The reports did not present the molecular and the clinical as distinct tests, where one is a gold standard measuring the efficiency of the other. Rather, the results from one type of test were simply added to the results from another type of test. And so after promoting (or is it demoting?) the molecular hits to passing clinical scores, they can then divide 69,016, the total population of the clinical test, by their combined 309 “clinical” results. Their result is the 1:223 found in the Corrigendum. But if we responsibly separate the two tests, calculate the results separately, consider the different population sizes, and then bring them back together on the same scale, what will we see?

We have two distinct diagnostic procedures, each with its own distinct population. There were 69,016 in the population who were clinically scored; of these, after excluding the Top4 molecular results, 209 were found to be “definite” or “probable.” That’s a rate of 1:330.2. But there were also 100 Top4 molecular hits, not all among these 69,016, but among the genotyped population of 60,710. That’s a separate rate of 1:607.1. Let’s combine these two into one procedure, as the authors did, but this time we will concern ourselves with the population size of each distinct test. We want to bring both tests alongside each other, at the same scale.

One way to do that is to convert both results to a per million ratio. The Top4 molecular hits would be 1,647.2 and the clinically passing scores (excluding the Top4) would be 3,028.5. Now we add the two to get 4,675.7 and 1 million divided by that 4,675.7, we get a prevalence of 1:213.87.

Another way to bring the two tests into the same scale would be to gauge the difference between the molecular and clinical test populations, then apply that difference, by subtraction, to bring one of the two populations and its FH determinations, to the same scale as the other. Since the molecular tests are

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41 All 100 Top4 were detected molecularly among the 60,710. A portion of these however will be found among the 69,016 clinically tested, which I estimate on page 73 to be around 15. We exclude all Top4 from the clinical test to avoid counting the originally passing scores twice in the step which follows. We will first establish a clean separation of the populations into an equally clean separation of the several constituents of the results: the Top4 on the one side, and the Ex-Top above clinical detection and the clinical false positives on the other side. The Ex-top4 below clinical detection were not included in this study, and this fact is central to my analysis.) If I opted for the other method, of keeping those Top4 which originally scored above clinical detection among then 69,016, then I must introduce a human factor – my estimate. Performing the math with such a clean separation removes my having to introduce, unnecessarily, this additional risk.
the gold standard and since that number is key to the deductive analysis I present, I will leave that number alone and adjust the clinical to an equal proportion. So 60,710 molecular tests is 87.965% of the 69,016 clinical tests, and so we then reduce the 209 by that same degree and have 183.85 results out of 60,710, alongside the 100 Top4 molecular hits out of 60,710. Now both tests are set against the same base, 60,710, and we divide by the 284 results of both tests (the 184 clinical, equalized, and the 100 molecular) and arrive at 1:213.77.

Accordingly, in the following pages we will downsize the 69,016 population and 209 of the clinical results by 12%, thus “equalizing” the 2 constituents of the 1st report’s results. Clinical “definite” and “probable,” to scale, will be 184, instead of 209. This works in the authors’ favor.

Opportunity for deduction: The same core population is carried over to the 2nd report

“This prevalence of FH is comparable to our previous report in a smaller sample of the same population based on phenotypic DLCN criteria alone.” ~ 2nd report, Benn, et al. 2016

Let’s lead in with a point that at first appears to be only quibble. The “smaller sample of the same population” was 60% of the total found in the 2nd report. That is, if I had 6 slices of a pie on a plate and then later added 4 more slices, I could reflect and say that at first the plate had less pie and that later it had more pie, but it should be understood that the original portion was much larger in comparison with the portion added.

As for the 1st report’s being solely phenotypic, that is not what it sounds like. Although the population of the clinical portion of the 1st report was 69,016, 60,710 of those were genotyped. “LDLR W23X, W66G, and W556S and APOB R3500Q mutations were genotyped in 60,710 individuals by TaqMan ....” (See page 123.) The study took the genotyped hits, gave them a clinical score, and thereafter regarded them as phenotypes. Culturally, the molecular results help justify a clinical procedure which in actual practice will lack the resources to screen an entire population, molecularly.

To the population of 60,710 genotyped in the 1st report, 37,290 were added for the 2nd report, now totaling 98,000. These are not studies of two completely separate populations; we should remember that the very same 60,710 individuals have been carried over to the subsequent report. This last point is crucial. The fact that both reports involve the very same 60,000 people presents us with a decisive deduction: the number of mutation carriers in the 1st report cannot possibly exceed those of the 2nd report. This reveals a deductive ceiling, above which the numbers are not credible.

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42 When I refer to 209 clinical results or the adjusted 184, I refer to the number of clinical results after excluding Top4 carriers. An undisclosed number of Top4 are necessarily shared between both constituents, and because we necessarily include them in the 100 Top4 molecular, we will leave them out of the Clinical total, so as not to count them twice. (We also avoid the risk of having to work with an estimate.) 309 – 100 Top4 molecular hits = 209 otherwise clinical results, after excluding Top4.

43 “FH” is used by the authors to mean “ADH” – it includes both FH LDLR and FDB APOB. See pages 120, 125 and 14.

44 In the 2nd report, the title, some illustrations, and the paragraph titled, “Results,” use 98,098. However, the detailed breakdown of unrounded numbers totals up to exactly 98,000. Elsewhere, other numbers are used. See pages 105 and 106 for details regarding this red flag.
**Deductive ceiling: 1st report’s key number**\(^{45}\) cannot be more than 25

Using deduction, let's break down the molecular hits in the 1st report into the *mathematical limits* of their original clinical scores – the numbers beyond which impossibility begins.

The corrigendum to the 1st report claims 309 Probable and Definite patients.

The 100 mutation carriers found in the 1st report were not affected by the Corrigendum, since they had received 8 points for their molecular status. Even after raising the cutoff point in the Corrigendum, any score 6 or higher was still counted into the results.

The 2nd report tells us that the number of detected TOP4 mutations which were *originally*\(^{46}\) in the Probable and Definite FH categories in the 1st report’s population, plus its own contribution, was 25. The 1st report is a slice, and the 2nd report adds another slice to the pie. Neither slice can be more than the whole of the pie: 25. *This is our “deductive ceiling”* for the Top4 originally above the detection point in the 1st report. The remaining 75, as the *minimum* mathematically possible, must have been below the clinical detection point. 75 is our “deductive floor.”

We now adjust the 209 clinical results in the authors’ favor to 184 in order to present both the molecular and the clinical results on the same scale, i.e., against the same population of 60,710. This is an adjustment of 12% (See page 64.)

Using the procedure of the 2nd report, the Top4 mutations actually found are estimated to make up 38.7% of total mutations. Then, 25 Top4 mutations ÷ .387 = 65 total mutations. 65 total mutations − 25 = 40 Ex-Top4 mutations. The 40 Ex-Top4 represent those mutations which would have been found among the remaining 184 clinical FH had all mutations types been screened for. 184 clinical FH − 40 ExTop4 = 144. Likewise, for the 75 Top4 below the detection point: 75 Top4 ÷ .387 = 194, then 194 − 75 = 119 Ex-Top4. These 119 are not subtracted from any numbers in this table because they were below the clinical detection level and because they were not targeted in molecular testing. *They are the deductive minimum of genuine mutation carriers entirely neglected in the 1st report.*

The remaining 144 are estimated to be the *minimum number of false positives mathematically possible, not an estimate of their actual number. The actual number will be worse.*

\(^{45}\) See pages 122 and 123 for source material.

\(^{46}\) “Originally” refers to the DLCN score *before* considering the mutation status.
The 2nd report serves as a “Rosetta Stone” for understanding the 1st report

The 2nd report attempts to confirm the prevalence of the 1st report. However, as my original analysis will demonstrate, it uses a different constituent to do so, and thus, after mathematical reconciliation, it deductively proves the 1st report was inflated with false positives.

The authors calculated the total number of mutation carriers: 174 ÷ .387 = 450. From here we use the total population of 98,000 to arrive at a prevalence of 1:217.78. The 2nd report provides the number of patients assigned a clinical score. For example, out of 98,000 individuals screened, 316 were assigned to the “probable” category. These are “above” the clinical cutoff point. The report also includes the number of patients within each category who were found through genotyping to carry one of the top four most prevalent mutations (“Top4”). So of the 316 assigned as “Probable FH,” 19 had one of the Top4 and so 297 did not. Also, in following the procedure used in the 2nd report, the Top4 are said to make up 38.7% of the total mutation spectrum and so we would estimate 30 remaining mutation carriers for the Probable category: 19 Top4 ÷ .387 = Total 49. Total 49 – 19 Top4 = 30. I refer to these 30 as “Ex-Top4.” Thus, 316 – 19 – 30 = 267 non-mutation carriers in the Probable category. Following this procedure, I have mathematically converted the results as follows.

Note: The majority of Top4 carriers are actually below “Probable” and “Definite” -- the clinical detection point. This fact will remain as an important premise within our final deduction.

<table>
<thead>
<tr>
<th>2nd report, Page 1387</th>
<th>Top4 Mutations found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical score</td>
<td></td>
</tr>
<tr>
<td>population</td>
<td></td>
</tr>
<tr>
<td>Below</td>
<td>90956</td>
</tr>
<tr>
<td>Cutoff</td>
<td>6703</td>
</tr>
<tr>
<td>Above</td>
<td>316</td>
</tr>
<tr>
<td>Cutoff</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>98000</td>
</tr>
<tr>
<td></td>
<td>174</td>
</tr>
</tbody>
</table>

Mathematical conversion of 2nd report results

<table>
<thead>
<tr>
<th>2nd Report Page 1387</th>
<th>Top4: 38.7% of Mutations</th>
<th>Derived</th>
<th>Non-mutation carriers</th>
<th>Remaining Ex-Top4: 61.3% of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>unlikely</td>
<td>66</td>
<td>unlikely</td>
<td>90785</td>
<td>66</td>
</tr>
<tr>
<td>possible</td>
<td>83</td>
<td>possible</td>
<td>6489</td>
<td>83</td>
</tr>
<tr>
<td>probable</td>
<td>19</td>
<td>probable</td>
<td>267</td>
<td>19</td>
</tr>
<tr>
<td>definite</td>
<td>6</td>
<td>definite</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Significantly, we had 341 in the Probable and Definite categories (table above) and I calculate a

47 The report used a prevalence of 1:217. I could not duplicate this number without breaking the rules that usually apply when rounding numbers. It appears that the authors used a population of 98,098 in the “Results.” I would then have to round down from a prevalence of 1:217.996. For more on population discrepancies, see pages 105 and 106.

48 See page 122 for screenshot.

49 As in the tables above, the report itself listed the higher scoring DLCN scores in the lower rows, and the lower scoring in the higher rows. For easy comparison, I will keep that orientation in my tables. However, when I write, “Above the cutoff,” I mean the higher scoring “Probable & Definite” categories in the lower rows and do not refer to the orientation and order of the table rows themselves. Conversely, when I say, “Below the cutoff” or “Below the detection point,” I mean the lower scoring categories, “Unlikely & Possible.”
maximum of 65 total mutation carriers (25 from the Top4 ÷ .387 = 65). This leaves 276 false positives among 341 determined clinically to be “FH.”

The basis of the 2nd report was molecular analysis and so this high false positive rate for the clinical scores is not an issue – for this 2nd report. However, we are going to reconcile this data with the 1st report and its Corrigendum. Since the 1st and 2nd reports share 60% of the same population, and since the results in the 1st report are presented as clinical, we can see from here that the bulk of the clinical false positives in the 2nd report would make up a large part of the “FH” patients identified in the 1st report.

341 total – 65 mutation carriers = 276 False Positives in DLCN Probable and Definite categories.

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50 19 probable + 6 definite = 25.
51 Again, we will deal later with the issue of the distribution of the Ex-Top4 among the clinically assigned categories: page 77.
What if we apply the 1st report’s method to the 2nd report’s data?

Now what if we decided to take the total hits of the top four most frequent mutations in the 2nd report, 174, and instead of calculating in the remaining less frequent mutations, we simply appended them to the remainder of those categorized clinically as “Definite” and “Probable”? (297 + 19 DLCN FH + 174 Top4 hits = 490.) See the table below to compare the two methods. (If the reader has an objection to what will follow, these alternating target populations are precisely the point.)

Using the 1st report’s method on the 2nd report’s data (right) would inflate the results with false positives, while swapping out genuine mutation carriers. The difference between the two procedures illustrated above is the problem in the 1st report. 60% of those in the 1st report are the same individuals we see here in the 2nd report. So we will soon be working with airtight deduction. All our objections to using the two prevalence rates above for comparison are also present in the actual reconciliation of the 1st and 2nd reports. The 1st report is supposed to be the source for the “Authoritative” report.

- Let us carry forward a key observation: where are the majority of mutation carriers? Probable & Definite FH or Unlikely & Possible FH? They are mostly short of the passing score -- mostly in the Unlikely & Possible clinical categories.

Using the 1st and 2nd report methods on 1st report’s deductive ceiling

In the previous section we compared the 1st and 2nd reports’ methods on the 2nd report’s data. Now let’s apply the two methods to the 1st report’s “deductive ceiling,” that is, the maximum number of Top4 which are mathematically possible originally above the clinical detection point. (See pages 65 and 66.) Given that the majority of mutations are found in categories below probable and definite, and given the procedure of the very
same authors’ 2\textsuperscript{nd} report, 144 of the 184 remaining clinical FH would be false positives.\textsuperscript{52} Using the deductive ceiling of 25 for the Top4 originally above the clinical detection point, let’s break down the 1\textsuperscript{st} report. After giving the authors the best footing mathematically possible, the data according to both methodologies is as follows:

Assuming the Ex-Top4 distribution among the clinical categories to be roughly similar to the Top4 and to other scientists’ results, we make the following deductions.\textsuperscript{53} Given the 2\textsuperscript{nd} report’s detailed breakdown, we see that the majority of mutation carriers were excluded from the 1\textsuperscript{st} report because they were not molecularly targeted and they were below the clinical cutoff. It was impossible for them to be at the same time included above the clinical detection point in the “FH” prevalence count of the 1\textsuperscript{st} report. Those mutation carriers below the clinical cutoff cannot also be those who are above the clinical cutoff. From one report to the other, patient populations are swapped. But the “FH” label remains consistent, creating an illusion that one FH total confirms the other. On the contrary, the latest prevalence number in the 2\textsuperscript{nd} report does not prove the source\textsuperscript{54} to the Authoritative prevalence count; it refutes it. It is deductively impossible for the 2nd report to correctly identify mutation carriers and for the 1\textsuperscript{st} report not to be inflated with false positives.

- \textbf{This is an analysis based on a deductive limit. Working with responsible statistical comparisons and estimates, the percentage of false positives will certainly be much higher.}

\textsuperscript{52} See page 64 for the adjustment of the 209 clinical results to 184. In brief, the 1\textsuperscript{st} report’s clinical results among 69,016 are now adjusted to the same scale as the molecular results, 60,710.

\textsuperscript{53} For treatment of the distribution of the Top4 and Ex-Top4 within the clinical categories, see page 77: “Weakest link in my analysis is nonetheless very strong.”

\textsuperscript{54} The source to the Authoritative report is supposed to be the 1\textsuperscript{st} report.
Again, any objection one might have in juxtaposing these two procedures together is precisely the point. These are the same two procedures used from one report to another, using 60% of the same population. We must accept that the false positives, at a minimum, are 51% of the total claimed to be “FH” in the 1st report \((144 \div 284 = 51\%)\). Given that the 75 below the clinical cutoff are, by that fact, clinically undetectable, the minimum number of false positives in a real-world clinical setting is here estimated at 69%. \((144 \div 209 = 69\%)\)

**Estimating the 1st report’s missing raw data**

Once we start working with estimates and deductive limits it is important to remember that the number of those “swapped” is a different issue from the fact that a swap took place. In the preceding section I demonstrated with mathematical rigor how the swap takes place and that this or that estimate is not the point. The swap is inherent in the methodology.

However, using examples can be a useful aid. So in the following pages I will present quantities. There are many ways to tease the numbers out of the authors’ material.

But again, my purpose here is to demonstrate a math-assisted swap and not a science-based estimate of FH prevalence. There is always a risk that the central argument will be lost in peripheral distractions: if we can see this or that basis for an estimate, then we have an easier-to-find conflict, and conflicts are the main literary vehicle for entertainment. We can then be distracted from the conflict-free deduction which underlies this analysis and which affords no room for debate.

Good math precedes solid scientific conclusion, and bad math precludes it. So the following pages will not be an attempt at scientific discussion but at illustrating the bad math. It is as if a telephone pole were down and after showing that, I then proceeded to illustrate that same fact, but this time by teasing apart and testing combinations of wires in the telephone box. If a dispute emerges surrounding “blue”
and “red wires,” “here” and “not there,” then it is hoped that the central issue of the downed telephone pole be remembered as the real target of the discussion.

A Guideline: We will estimate the mutation hits *originally* above the clinical detection point.

Heretofore we have given the 1st report the best possible footing: working with a deductive ceiling ... the *maximum* amount of Top4 mutation carriers that could exist above the clinical cutoff used for the 1st report: 25. However, that number would require that there be zero Top4 hits for the next 40,000 added to the 2nd report. We would find roughly 1 in every 2,400 in the 1st report’s 60,000, and then after scanning the next 40,000 we would find zero mutation carriers that scored at the DLCN definite and probable. This is of course unrealistic.

So then, how can we keep estimates in a responsible range? We try to remember not only the estimate for the 1st report but also the consequences such a number would have for the 2nd report. We can’t allow too much for the one without leaving the other ridiculous.

The following chart demonstrates the interdependence that estimates have within the 1st and 2nd reports. The more hits for the Top4 originally above the clinical detection level that one estimates for the 1st report, the fewer one has for the 2nd report. We also track the resulting false positive percentage, using a practical setting. (IE, we don’t assume that molecular testing will take place for an entire population, but only on the pool isolated by a passing clinical score.)

Note that the 60-40 proportion -- the 1st report’s population compared to what was added to the 2nd report -- results in a real-world, false positive rate of 80.5%. This estimates only 15 Top4 hits originally above clinical detection.

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60/40 proportion matches 1st report to 2nd report addition. This estimates 15 Top4 above the cutoff.

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55 See page 124 for False Positive percentages under different scenarios.
Estimates of the 1st report’s molecular hits which originally scored above the clinical cutoff

<table>
<thead>
<tr>
<th>Estimated TOP4 for 1st report which scored DLCN Probable or Definite.</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.5</td>
<td>First, given that 60,710 from the 1st report have been carried over to the 2nd report, and that the 2nd report adds 37,290 to arrive at 98,000, it would not be unreasonable to work with a 62% reduction of the 2nd report and compare that to what we were told in the 1st report. There were 25 in the Top4 at the definite and probable categories in the 2nd report and 25 \times .62 gives us an estimate of 15.5 for the 1st report. We make no claim for precision, but this statistical reduction to 15.5 for the 1st report makes more sense than making no reduction at all. This also means that of the 100 Top4 mutation carriers detected in the 1st report, about 84.5 are estimated to belong to categories below the clinical detection point.</td>
</tr>
<tr>
<td>14.5</td>
<td>In the 1st report, we can easily subtract the 100 Top4 mutation hits from the 284 total results.(^{56}) Now the 184 derived no longer includes the Top4, but does include some of the Ex-Top4. We need to stay parallel when deriving our ratio from the 2nd report, so we exclude the Top4 and keep in the Ex-Top4. Here are our first two steps. The 2nd report’s total of Definite and Probable (at this point, regardless of mutations present or absent), subtracted by the Top4 detected: 341 – 25 = 316. Then 25 ÷ 316 = .079. And in the final step, applying the same percentage to the 1st report’s 184, a derivation which likewise excludes the Top4 but not the Ex-Top4: 284 -100, and then 184 \times .079 = 14.5</td>
</tr>
<tr>
<td>14.4</td>
<td>Calculate the ratio of the 2nd report’s Definite and Probable Top4 to the total Top4 found: 25 ÷ 174 = .144. Compared to the total Top4 found in the 1st report: 100 \times .144 = 14.4</td>
</tr>
<tr>
<td>15.5</td>
<td>Calculate the proportion of the Top4 at the Definite and Probable categories to the total population involved: 25 ÷ 98,000 = .0002551. Apply this proportion to the total of the 1st report: 60,710 \times .0002551 = 15.5</td>
</tr>
</tbody>
</table>

**Average of 15**

At an estimate of 15 Top4 hits, originally above the clinical detection point, a real world false positive rate works out to 80.5%

<table>
<thead>
<tr>
<th>Reasonable estimate for Top4, Accepting that screening is impractical below clinical cutoff</th>
<th>Top4 detected</th>
<th>Ex-Top4 derived</th>
<th>Minimum False Positives</th>
<th>Relevant Population</th>
<th>False Positive %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Top4 available above the clinical cutoff.</td>
<td>15</td>
<td>23.8</td>
<td>160.2</td>
<td>199</td>
<td>80.5%</td>
</tr>
</tbody>
</table>

Let’s plug in our estimates and view the breakdown through the 1st report’s method. For our estimate of the Top4 mutation carriers which scored above the clinical detection point, we are going to give the 1st report the best footing possible. Instead of taking the average of 15, we’re going to remember that

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\(^{56}\) See pages 64 and 123
we’ve adjusted the 1st report’s clinical scores in order to work in an equal population scale to that of the molecular results. (See page 64 for details.) We want to leave as little room for doubt as possible. So although this only affects the 14.5 estimate above, we will nonetheless add the 13% back in, always conscious of tilting grey areas in the favor of the authors. The higher this number the _lower_ the false positives in the result. We will use 17.

With this, let’s estimate the full mutation spectrum of the 1st report according to the ratio used in the 2nd report (.387).^{57}

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^{57} For treatment of the distribution of the Top4 and Ex-Top4 within the clinical categories, see page 77: “Weakest link in my analysis is nonetheless very strong.”
Two different “FH” populations alternate between the two reports.

Using an estimate of 17 Top4 above clinical detection point: Viewing the 1st report’s numbers according to the 2nd and 1st reports’ methods.

This allows us to see that the 2nd report, far from being a confirmation of the 1st report, suggests that the 1st report is inflated with false positives\(^58\) and that false negatives\(^59\) are neglected. The false positives are in effect “renamed” through the methodology, if the reports influence the medical community to accept clinical screening as sufficient. The false negatives, being inaccessible, simply do not exist on the clinical “radar screen.” The vast majority of the False Positives shown here make up the “True Positives” behind the Authoritative report.

Not the same people: The majority through each of the reports’ different methods are different people. Both prevalence methods, when applied to the 1st report, share the same 100 molecular results from the top four most frequent mutations. And both share the same 27 remaining mutations as calculated by their respective proportions of the full mutation spectrum – the technique used in the 2nd report. Thus 127 individuals are shared between the two methods. We must accept by deduction that the 131 False Negatives below the cutoff and absent from the 1st report cannot also be the 157 so-called “True Positives” above the cutoff in that same 1st report. The two reports are working with the same 60,000 people and so this is a deductive conclusion. The similarity in the prevalence numbers between the two reports is a coincidence and declaring their “comparability” cannot be correct.

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\(^{58}\) Those who look like FH but who do not carry a mutation.

\(^{59}\) Those who do not look like FH but who do carry a mutation.
2nd report's method on 1st's data: those who are different people.

The non-targeted mutation carriers who were also below the cutoff point. These could not have been in the 1st report's total: 131.

Both reports share some of the Molecular results.

Probable & Definite Top4 were 100.

Ex-Top4 above the cutoff is estimated to be 27.

1st report's method on 1st's data: those who are different people.

Of 184 who were not Top4 molecular hits, only 27 are estimated to be Ex-Top4, leaving 157 which would not be mutation carriers.

2nd report's method on 1st report's data

131 are different people

127 same people

157 are different people

The two reports are mostly of different people.
Regeneron’s Science magazine article supports my analysis of the Danish reports

I wrote the following content before Regeneron published their report. **With this recent report, we can clearly see that the vast majority of those given passing clinical scores are not found to carry a mutation, and the majority of those who are molecular hits do not have passing clinical scores.**

However, I will keep this chapter here as additional proof of the variability of the FH phenotype. In fact, the variability is so great that it is even questionable if there is such a thing as an unequivocal “FH phenotype.” **Without a defined phenotype, clinical scoring systems are not sufficient to identify an FH mutation carrier.**

Here’s why I previously felt it necessary to include this chapter: for my mathematical proof, there was one necessary assumption which was outside of the safety of deduction. However, scientific evidence, much of it provided by the very authors, showed this link to be nonetheless very strong. What follows is my original presentation regarding FH phenotypic variability.

**Weakest Link in my analysis of Danish reports is nonetheless strong**

**Weak Link:** A very large percentage of the Ex-Top4 could have originally been above the DLCN Cut-off.

**Decisive Reports:** Fouchier, et al, put together a report titled, “The molecular basis of familial hypercholesterolemia in The Netherlands.”

It was an exhaustive hunt for mutations among the population. Thus, they included many more mutations than their “Top 4” most frequent mutations. Here is one of their conclusions. (The emphasis is mine.)

> Although mutations in specific domains of the LDL receptor gene impair specific functions of the corresponding domain in the LDL-receptor protein, **this can only partly explain the striking variable phenotypic expression of the disease. Different mutations in the same domain and even the same mutation in different patients show large differences in clinical phenotype.** For example the most frequent mutation in the Netherlands, the N543H/2393del9 bp, exhibits a phenotype ranging from an almost

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60 See page 62.

61 As shown in the screenshot above, Table 1 of the 2nd report listed the higher scoring DLCN scores in the lower rows, and the lower scoring in the higher rows. However, when I write, “Above the cutoff,” I mean the higher scoring Probable & Definite categories. When I say, “Below the cutoff” or “Below the detection point,” I mean the lower scoring categories, Unlikely & Possible.
normal LDL cholesterol to LDL cholesterol levels far above the 95th percentile (Umans-Eckenhausen MA, et al. submitted). With such an extent of variability in the clinical expression, it is evident that other genes and environmental factors must be involved. Examples of such genes include cholesterol ester transfer protein (CETP) gene, lipoprotein lipase (LPL) gene and the apolipoprotein E (apoE) gene (Boer et al. 1998; Kastelein et al. 1999; lipoprotein metabolism influence lipoprotein levels, but only partly explain the striking variability in phenotypic expression. Environmental factors, such as lifestyle habits, and familial risk factors for cardiovascular disease are of great influence in determining the clinical outcome of FH, as recently demonstrated (Sijbrands et al. 2000, 2001; Umans-Eckenhausen MA, et al. submitted). ~ IBID.

And another report on The Netherlands by Sjouke, et al, specifically focused on “Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome.” It shows a parallel argument where the clinically diagnosed HoADH (HoFH) will result in a patient pool inflated with HeFH. And this is because the phenotype is much more varied than previously thought, with many of the HoADH scoring below the usual clinical cutoff: “Surprisingly, only 50% of the patients met the clinical criteria for hoADH (LDL-C .13.0 mmol/L) ...”

It concluded: “… the clinical phenotype is more variable than previously assumed.”

In the discussion: “We also observed a significant phenotypical variability in patients diagnosed with molecularly defined hoADH and, in particular, the majority of patients did not fulfil the phenotypic criteria for hoADH.”

The emphasis in the passage below is mine.

Phenotypic diagnostic criteria have been used to diagnose hoADH, and LDL-C levels .13.0 mmol/L are generally accepted as a major criterion for the presence of hoADH. It is of note, however, that a minority of patients in our study met this criterion, and the range of LDL-C levels (4.4–21.5 mmol/L) in our study overlaps to a significant extent with LDL-C levels observed in heterozygous ADH patients. Interestingly, we identified a total of 69 heterozygous ADH patients [of 13 080 patients (0.53%), of whom 6 index cases] with untreated LDL-C levels . 13 mmol/L in the database of the Foundation for the Identification of Persons with Inherited Hypercholesterolaemia. Based on the clinical criteria, these patients should be considered to suffer from homozygous ADH. This clearly further shows the overlap between heterozygous and homozygous ADH. The potential misperception that a patient with LDL-C levels much lower than expected for hoADH cannot be a carrier of two pathogenic mutations has likely resulted in an underestimation of the prevalence of hoADH. It is therefore no surprise that lipid levels in our study were on average lower than generally assumed in hoADH patients. Moreover, LDL-C levels observed in our study were also significantly lower than observed in a large retrospective cohort study in hoADH patients performed by Raal and co-workers. In their study, comprising 149 hoFH patients, LDL-C levels were 16.4+3.9 mmol/L and the mean age of hoADH patients in this South African cohort was 26.8+14.6 years, compared with a mean age in our study of 37.4+19.2 years. The majority of patients in the South African study were molecularly diagnosed with hoADH. The large difference with our study is the fact that, in their study, sequencing of LDLR
and APOB was only performed upon a clinical suspicion of hoADH. The latter will result in an inflation of the clinical phenotype associated with the molecular defect.” ~IBID.

These are exhaustive studies and were not limited to a few of the most frequent mutations. Variability includes “a majority of patients [who] did not fulfil the phenotypic criteria for hoADH,” the most severe form of FH.

There are other points to be made. First, overturning my thesis would require an inverse statistical outcome to what we know already. The majority of the Top4 have already revealed themselves to be below clinical detection. On what basis would we assume a concentration of the Ex-Top4 above the cut-off and not the distribution of the spectrum evident thus far? 62 It would be highly improbable. The 2nd report shows that 149 out of 174 Top4 mutation carriers were below the cutoff. (See illustration on the left.) These same Top4 mutations show great variability in gene expression.

Additionally, it would defy the aim of the report for the authors to keep silent here. Strengthening their case, why then put in the extra effort to omit this data? All their declared difficulty in genotyping would have been wrong; the clinical cutoff used would have resulted in a target-rich pool of mutation carriers. Did they miss such an opportunity for a decisive result? ... Or is it just that most Ex-Top4 mutation carriers are like Top4 mutation carriers? Out of reach due to variability in the mutation effects, with large numbers of them too mild to be detected clinically.

The results revealed in the 2nd report are not the only evidence showing that environmental factors play a large role in the FH phenotype, producing great variability. Three of the very same authors of the 1st

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62 By “Ex-Top4” I mean the remainder of the spectrum besides the four most frequent, or to put it differently, those ADH mutations which were not targeted in the studies. See page 121.
and 2nd reports produced an *Earlier Report* where they showed that three of these four most frequent mutations had a range of clinical phenotypes, concluding that environmental factors play a significant role.

“Because the type of LDLR mutations were the same in carriers identified in the 3 different background populations, the increase in cholesterol levels in the patient groups was not caused by an effect of the LDLR mutations, but could be attributed to both “environmental factors,” such as dietary intake and obesity, and to other minor mutations that modulate the cholesterol phenotype in the IHD and FH populations in general.”

They also held out the possibility that ...

*In heterozygotes identified in the general population, a different genetic makeup or environmental factors could counteract the effect of LDLR mutations by reducing synthesis or increasing breakdown rates of LDL, resulting in lower cholesterol levels. However, differences in cholesterol levels between probands identified in the general population or among patients with IHD or FH could not be explained by differences in type of LDLR mutation, because these were the same and could also not be explained by differences in the most obvious confounders ....*

On the left is another conclusion of variability in gene expression found in “LDL-Receptor Mutations in Europe,” by Dedoussis, et al.

There are many sources to cite. Here are some others.

“FH is a disease that shows great phenotypic variability.” ....

“Due to the paucity of data on genotype phenotype correlations, clinical diagnosis will miss a large percentage of FH patients. It is currently estimated that only 15 to 20% of patients with FH are actually diagnosed. A study on 643 Danish probands could not even find a single phenotypic characteristic to predict the existence of a mutation.”

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63 The four most prevalent mutations used in the 1st and 2nd reports include the APOB mutation. This passage is about LDLR, and so it mentions only the top 3 most frequent LDLR. The APOB is irrelevant here. Table 1 of the 2nd report shows that the APOB mutations also have great variability, with most of them scoring below the clinical detection point.

64 Phenotype of Heterozygotes for Low-Density Lipoprotein Receptor Mutations Identified in Different Background Populations; Anne Tybjærg-Hansen, Henrik Kjæruff Jensen, Marianne Benn, Rolf Steffensen, Gorm Jensen, Børge G. Nordestgaard 2005

65 Ibid.

66 Familial Hypercholesterolemia: The Lipids or the Genes? Akl C Fahed and Georges M Nemer; 2011
“For all other patients with FH caused by LDLR defects, environmental or other inherited factors seem to be more important than the type of mutation in determining the phenotype severity.” 67

“Consequently, the phenotype of FH individuals is highly variable, probably also due to environmental factors and other genetic polymorphisms influencing the clinical outcome of FH.” … “We here present a large, descriptive study of 1038 Danish FH individuals, who display a wide variety of phenotype regardless of mutation status.” … “Conclusions: No parameters could decipher mutation status a priori. All individuals fulfilling the FH criteria should therefore be referred in order to facilitate family tracing and genetic counseling.” 68

There is a famous study of Canadian Chinese who suffered harmful effects of FH. Their relatives in China were tested, and those found with identical mutations nonetheless “do not have a markedly elevated concentration of LDL.” 69 The study concluded with the strong suggestion that environmental factors play a large role in phenotypic expression of the disease. How high or low would a mutation carrier score during clinical screening? “It has been shown that different environmental factors may moderate the phenotype in heterozygous FH.” 70 We are not just talking about the variety of mutations, but the simultaneous variation of clinical scores among patients with the same mutations.

And APOB is typically milder than LDLR, and it makes up the majority of molecular results in the 2nd report. Here is another paper, saying essentially the same thing:

“Familial defective apolipoprotein B (FDB) caused by the R3500Q apolipoprotein B gene mutation may mimic FH but the clinical course, however, is often milder than that seen in patients with LDL receptor gene mutations.” 71

It would seem highly improbable that all of the following would occur:

1. That The Netherlands’ exhaustive demonstration of “striking” and “surprising” phenotypic variety would not generally represent that of neighboring Denmark.
2. That among the entire Ex-Top4 spectrum there would be no phenotypic variety from one named mutation to the next but that each type would be at the highest intensity of disease.
3. That among those with the same Ex-Top4 mutation there would be no variation of intensity of the disease but all cases would be at the highest intensity.

We would expect an equally wide distribution among the Ex-Top4 mutation carriers. It is either that or variety would have to stop, without precedent.

67 Mechanisms of Disease: genetic causes of familial hypercholesterolemia; Anne K Soutar* and Rossi P Naoumova 2007
68 No certain predictors for mutation status in a Danish cohort with familial hypercholesterolemia: A descriptive study Mads Nybo, Klaus Brusgaard, Annebirthe Bo Hansen; 2007
70 Ibid.

81
Anatomy of the Publication Strategy

If an alarm sounds and everyone sees only one exit, where will they go?

Selective publishing of a Selection Bias:

1. The default use of clinical scoring systems (for example, DLCN) is \textit{not sufficient} to determine FH ...
2. ... and the majority of passing scores are false positives ...
3. ... and these clinical scoring systems filter out the majority of genuine mutation carriers.
4. All the while, the authors nonetheless declare that these clinical scoring systems are \textit{recommended} and \textit{common practice} ...
5. ... and in the next breath use genetic studies to prod the medical community with the urgency of “underdiagnosis!” ...
6. ... through the only available door ... \textit{clinical scoring systems}.

Here is a press release by Regeneron Genetics Center, and others, announcing the article: “Geisinger and Regeneron study finds life-threatening genetic disorder is substantially underdiagnosed” \textsuperscript{72} And in the report itself, “A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network (DLCN).”

Analogy: The Prison Warden who shouts “forensics” in order to prod others to their default reliance on circumstantial evidence.

As a matter of epistemology, clinical scoring is to FH diagnosis what circumstantial evidence is to legal conviction. To use an analogy, imagine that a prison warden gets paid by the number of prisoners kept. We are in the early days of forensic science and there is a poorly understood crime. In fact, in a recent survey, less than 30% of detectives could recognize the crime from a case study. For the warden, this general ignorance is not a danger; it is an opportunity to “educate” those charged with apprehending criminals. He hires experts which use the credibility of forensics in a demonstration, not to expose the gross errors of relying on circumstantial evidence, but only to prove that many of the real criminals are “getting off scot-free,” knowing full well that detectives in the field don’t have the requisite infrastructure and that they can and will only avail themselves of their inherited, poorly understood reliance on circumstantial evidence. (So ironically, the reason why so many real criminals go free is in part because of the prevailing cultural reliance on circumstantial evidence.) It was the expert’s duty to correct the misunderstanding, and so to protect himself, he adds in a verbal disclaimer, with euphemisms like, “limitations to circumstantial evidence,” and using the word “caution” with the worst example of failed evidence imaginable, which was nonetheless used in his presentation as proof that large numbers of criminals are running free. Culture is a fait accompli, and so the mild disclaimers have no effect on the prevailing use of circumstantial evidence. However, the disclaimer does take the edge off of professional and legal criticism. That brief disclosure aside, he returns to the call for action, “dangerous criminals are getting away with it” and then tells the detectives, “circumstantial evidence is standard practice and we recommend it.” He earns his pay by putting greater force behind the prevailing cultural bias, which does all the downstream work for the Warden.
Actuality: Big pharma uses genetic studies in order to prod others toward their default reliance on clinical scoring systems

Big pharma gets paid by the number of patients it can locate for its drugs. They hire experts which use the credibility of genetic studies in a demonstration which stresses, not the gross errors of relying on clinical scoring systems, but use genetics to prove that many genuine mutation carriers are not being treated, knowing full well that their listeners can and will only avail themselves of their inherited, poorly understood reliance on clinical scoring systems. All the while one of the main reasons why so many mutation carriers are passed over is because of the inaccuracy of relying on clinical scoring systems. It is Big pharma’s duty to correct the misunderstanding, and instead, its cherry-picked and funded experts usher in the sense of urgency – “Underdiagnosis” and “patients are being passed over” – putting greater force behind the prevailing bias to do the rest of the work. To protect themselves, the experts add in disclaimers, with euphemisms like, “limitations to clinical diagnosis,” and choosing the word “caution” when using the worst case of APOB founder effect in the world as part of the proof of underdiagnosis. Culture is a fait accompli, and so the disclaimers have no effect on the prevailing use of clinical scoring systems, a species of circumstantial evidence. However, the disclaimer does take the edge off of professional and legal criticism. We have clinical diagnosis of a genetically inherited disease. Perniciously, the respect and confidence that goes with the accuracy and precision of forensic, genetic-based testing, actually aides the cultural use of the scoring systems, because now the underdiagnosis is a verified emergency and so we must make-do with what tools we’ve got.
Publication Strategy in Action: *Push Clinical Diagnosis* while shouting the alarm of “underdiagnosis.”

What follows are screenshots of the reports which used manipulated data and which are at the center of my analysis. The strategy is to motivate through a sense of urgency with a *genetic*-based claim of “Underdiagnosis” while continuing to promote clinical DLCN criteria as sufficient and standard practice.


Nordestgaard, et al. 2013

Motivate through a sense of urgency with “Underdiagnosed” while continuing to promote clinical criteria and diagnosis as standard.

Conclusion
Owing to severe underdiagnosis and undertreatment of FH, there is an urgent worldwide need for diagnostic screening together with early and aggressive treatment of this extremely high-risk condition.

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Conflict of interest: Consensus Panel members have received lecture honoraria, consultancy fees and/or research funding from Aegerion, Astra Zeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron.

The DLCN criteria are recommended in order to establish the clinical diagnosis of FH (Table 1). Among individuals with a definite or probable diagnosis of FH (DLCN > 5), and particularly those with an obvious clinical diagnosis with hypertension and/or high cholesterol plus a family history of premature CHD, molecular genetic testing is strongly recommended. When a causative mutation is found in the index case, a genetic test should be offered to all first-degree relatives (Figure 7).

To date, the prevalence of FH has not been assessed directly in an unselected sample from the general population. Using the Copenhagen General Population Study, an unselected European general population sample comprising 69,016 participants with heterozygous FH was diagnosed using the Dutch Lipid Clinic Network (DLCN) criteria (Table 1). The prevalence of individuals classified with definite or probable FH combined (DLCN criteria, ≥6 points) was 1/200 (Figure 2). Interestingly, prevalence for definit
Benn, et al. 2012

Motivate through a sense of urgency with “Underdiagnosed” while continuing to promote clinical criteria and diagnosis as standard.

**Context:** The diagnosis of familial hypercholesterolemia (FH) can be made using the Dutch Lipid Clinic Network criteria. This employs the personal and family history of premature coronary artery disease and hypercholesterolemia and the presence of a pathogenic mutation in the low-density lipoprotein receptor (LDLR) and apolipoprotein B (APOB) genes.

**Conclusion:** The prevalence of FH appears to be higher than commonly perceived in a general population of white Danish individuals, with at least half of affected subjects not receiving cholesterol-lowering medication. The very high risk of coronary artery disease irrespective of use of medication reflects the extent of underdiagnosis and undertreatment of FH in the community and primary care. *(J Clin Endocrinol Metab 97: 0000–0000, 2012)*

Translate this into: There is no universally accepted clinical criteria for the diagnosis of HoFH because the results of the disease are too varied. Failing to give genetic testing an adequate place in the debate, the logic ends up something like, “This supermarket scale doesn’t work so we’ll just have to use it.” FH is a genetically inherited disease. How it manifests itself outwardly very often does not look like clinically determined “FH.” Therefore, the definitive means of identifying FH exists. It is just that identification is through genetic identification:

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73 [https://www.sec.gov/Archives/edgar/data/827809/000082780917000012/nvln-12312016x10k.htm](https://www.sec.gov/Archives/edgar/data/827809/000082780917000012/nvln-12312016x10k.htm)
“The underlying molecular defect of FH consists of mutations in the gene coding for the LDL-receptor protein, detection of which provides the only unequivocal diagnosis.” ~ Aalst-Cohen, et al.74

The importance of establishing the identity of a causative mutation in an index case lies in the certainty that it provides an unequivocal diagnosis in that family, thereby permitting the identification of affected family members at a much younger age and optimizing the health benefit accruing from initiation of treatment as early as possible. ~ Liyanage, et al.75

A molecular diagnosis, i.e. demonstration of a pathogenic mutation in the LDL-receptor gene, therefore establishes an unequivocal diagnosis.76 ~ Fouchier, et al.

The gold standard of diagnosis is the identification of the underlying genetic defect, which is possible in 80% of cases and enables the identification of affected relatives of the index patient. ~ Klose, et al.77

Genetic testing … “genotyping” is resisted because it is not profitable:

“… genotyping may be required in some countries, reducing the number of patients diagnosed with HoFH.” ~ Novelion Therapeutics Inc., Dec. 2016 10-K78

With the preceding quotation, Novelion is clearly telling us that a clinical scoring system outsells a genetic identification procedure. There is no established criteria, and so why use criteria? Answer: Because the default to failed scoring systems is genetic testing, which is less profitable for Big Pharma.

74 Diagnosing familial hypercholesterolaemia: the relevance of genetic testing, Emily S. van Aalst-Cohen, et al.
75 Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution, Khemanganee E. Liyanage, et al
76 The molecular basis of familial hypercholesterolemia in The Netherlands, Sigrid W. Fouchier, et al.
77 Familial Hypercholesterolemia: Developments in Diagnosis and Treatment, Gerald Klose, et al.
78 https://www.sec.gov/Archives/edgar/data/827809/000082780917000012/nvln-12312016x10k.htm
The FDA makes a clear rejection of Nonfamilial Hypercholesterolemia

“Familial” means “inherited.” “Nonfamilial” means “uninherited.”

a) The FDA clearly rejected the inclusion of the Nonfamilial disease during the approval process. With this rejection, pharma had essentially asked, “Does it matter if drug candidates actually carry a mutation or is high cholesterol enough?”

b) And the answer was more or less, “Yes it matters if they carry a mutation, and no, high cholesterol is not enough.”

It follows by rational argument.

1. Pharma explicitly asked for both the Familial and Nonfamilial indication.
2. The FDA responds, No, only Familial. Nonfamilial is rejected from the proposed indication. So this is after a direct consideration.  

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https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000SumR.pdf

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79 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000SumR.pdf
OmedaRx, a national pharmacy benefit manager, says that Nonfamilial is to be considered “not medically necessary.”

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**Omedarx.com Position Statement**

III. Alirocumab is considered not medically necessary when used for:

A. Non-familial hyperlipidemia/ hypercholesterolemia

B. Primary prevention of atherosclerotic cardiovascular disease (ASCVD)

C. Primary prevention of ASCVD in patients who are statin-intolerant

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Unfamiliar terms give a margin for misunderstanding which common sense would never allow.

The outline of the FDA-Pharma dialogue is something like this:

1. Can I give this benefit to both the mutation and non-mutation carriers?
2. No, it’s not just a benefit; it is also a risk. The non-mutation carriers would be put at unnecessary risk because it appears that other options are available. The mutation carriers appear to have very few options. Therefore, you can give the benefit along with that risk to the mutation carriers, but we do not want to put the non-mutation carriers at risk unnecessarily.

However, the industry has skipped over this rationale. What they have been told not to do is synonymous with what they say they are doing.

Definitions of Variables and Synonymous Usage

| Definition | FH = Familial Disease = those who inherited a particular mutation. |
| Definition | Non-FH = Nonfamilial Disease = those who did not inherit a mutation. |
| Definition | P = Both FH and Non-FH. “P” stands for Phenotype, those who look like FH, whether or not they actually carry a mutation. There are both mutation carriers and non-carriers in this set. |
| Definition | C = P, where “C” stands for passing clinical scores and selects those who look like FH. |
| Synonymous | To ask “Both FH and Non-FH?” is to ask, “P?” It is also to ask, “C?” |

Dialogue:

Pharma asks: “Both FH and Non-FH?”
FDA answers: “No, only FH.”
Synonymous: “Not P.”
Synonymous: “Not C.”

Pharma however takes that last step out.

Contradiction: “Not C.” We’ll just skip the logic and recommend clinical scoring anyway. No one will notice.

The medical community is in a state of contradiction. Clear thinking precludes clinical scoring systems.
Contradiction and Off-label Marketing

“A study on 643 Danish probands could not even find a single phenotypic characteristic to predict the existence of a mutation.”81

1. If the set \{FH and Non-FH\} is requested,
2. And if Non-FH is rejected,
3. Then the set \{FH and Non-FH\} is rejected.
4. Consistent with clear thinking, all subsets within \{FH and Non-FH\} which include at least some Non-FH are also rejected.
5. Both passing clinical scores and phenotypic FH, as if sufficient, represent the set \{some of the FH and large numbers of Non-FH\}.
6. Therefore, both passing clinical scores and phenotypic FH, as if sufficient, are rejected.
7. If the FDA accepts clinical FH scoring systems that guarantee large percentages of Non-FH, they contradict their rejection of the requested set, \{FH and Non-FH\}.
8. If the FDA rejects the set \{FH and Non-FH\}, then they reject the results of clinical scoring systems.
9. Thus, the results of clinical scoring systems are off-label.
10. The promotion of clinical scoring systems is the promotion of off-label drug sales.
11. The deceptive conflation of Non-FH with FH and the proposal of lower diagnostic standards aggravates the violation of off-label promotion.

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81 Familial Hypercholesterolemia: The Lipids or the Genes? Akl C Fahed and Georges M Nemer; 2011
The parfait accompli of Information Dependence

The medical profession is a chain of linked expertise, where academic discovery – whether verification or falsification – is the uppermost link. Clinical practice hangs on the expert opinions of their tested procedures.

The FDA had already been circumvented when it said, “No,” to Non-FH by singling out FH. Pharma’s trick was to rename the disease far enough upstream such that the patients swapped in are regarded as on-label with the same downstream acceptance as a Robin accepts the Cuckoo chick to be its own. To switch metaphors, the FDA sends the drug to the clinical door with “FH” painted on it – but the patients on the other side of that door, “FH,” have already been swapped.

82 Non-FH means uninherited high cholesterol and stands for “Nonfamilial Hypercholesterolemia.” See page 89 for a treatment of the FDA rejection of Non-FH.
Evolution of Publication Strategies for Off-Label sales:

A named-disease is a kind of umbrella-top seen from above, and who that named-disease actually refers to walks under that umbrella. The old publication strategies sought to extend the drug’s use to other ailments. It begins after FDA approval, downstream. There is an umbrella with disease “A” painted on top, and another umbrella with “B” painted on top. The drug is only approved for those under the umbrella with “A” painted on it. Pharma uses its approval for one named-disease to cross-sell to another, unapproved named-disease. This is off-label marketing.

The new publication strategy seeks to extend the patient selection procedure, invisibly redefining patients, to bring other ailments under a single label.

The strategy seeks inaccuracy in order to widen a single umbrella, and keep the same paint on top, “FH.” Now it brings other diseases from under their own umbrellas to share this same umbrella. Under this single “FH” umbrella there are now non-FH. This occurs upstream from the FDA’s involvement. This is on-label only as far as community consciousness has accepted the upstream redefinition of what goes by the name of “FH.”

The old publication strategy took place after FDA approval. The new publication strategy begins before the FDA’s involvement. So later the FDA approves the PCSK9 drugs for HeFH, and, in name only, rejects pharma’s attempt to put Non-inherited Hypercholesterolemia on the label: clinical scoring systems guarantee that large numbers of prescriptions will go to Non-inherited Hypercholesterolemia.
What the illusionist sees is not what the audience sees: phenotype versus genotype

Molecular technology shows that the phenotype is more varied than previously thought. In fact, it would be more appropriate to say that there is no “phenotype.”

With no phenotype for FH, why did phenotyping become the dominant diagnostic strategy for FH?

Below:

- FH = Inherited Hypercholesterolemia.
- Non-FH = Uninherited Hypercholesterolemia.
- Not-H = not hypercholesterolemic.

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**Early Theory of Genetic Defect**

- Theory: there must be an inherited genetic mutation in the LDL-receptor. It explains high cholesterol in some people. We’ll call this “FH.”
- We have an idea of what it should look like: a “phenotype.”

**Molecular Finding**

- Molecular technology reveals unexpected clinical variety. The phenotype is more varied than previously thought. In fact, it would be more appropriate to say that there is no “phenotype.” Both carriers and non-carriers have both high and low scores.

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**Publication Strategy: Recover Bias**

- So for a genetically inherited disease – genotype - why is phenotyping the prevailing diagnostic procedure in the USA? Because it is more profitable. Non-FH were specifically eliminated from the FDA indication. As genotypes, it is clear that they are off-label. If the phenotype prevails, then many of the Non-FH can be “FH” merely because they look like FH.

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**Insufficient molecular technology to see under the clinical umbrella.” We cannot confirm and bring into focus true genetic prevalence.**

**On the left, many clinically scoring “FH” are not FH at all. And on the right, many who do not score as “FH” are FH.**

**Recovered Bias = 2 times the sales versus ½ the sales.**

**Clinical detection can’t find these. It is difficult and expensive to find them... and even if they were found, their low clinical scores mean that they may not need medication.**

**Somebody must discourage molecular technology as the gold standard. It would cut revenue in half. However, it is best to leave this avenue open so that pharma can add these to those found clinically, then pharma profits from both.**
Conclusion

1. **Regeneron’s prevalence claim is false.** (So are the prevalence claims of the 1st and 2nd Danish reports.) The linguistic conflation of diverse diseases (FH + FDB + FH3 + p.Arg3558Cys as “FH”) does not increase the number of disease carriers. After we tease each constituent back out and compare them, like for like, each with its own established rate, FH-as-LDLR is not “twice” what was commonly thought, nor is FDB-as-R3500Q. And in fact FH-as-LDLR in the Regeneron report is lower than the established prevalence. Here is an analogy: If Study A declared a prevalence of 10 million horses in the world, and Study B declared a prevalence of 20 million. Study B could say, “Horses are twice as prevalent as Study A thought them to be” -- unless it was revealed that Study A counted only horses, of the sort that are or can be domesticated, while Study B included zebras along with the horses, calling all of them “horses.” In one study zebras are not “horses,” while in the other study zebras are “horses.” It is deceptive to claim twice the prevalence when the only difference is in the linguistic re-definition and conflation of zebras with “horses.” To be in good faith, Study B’s focus should not be on prevalence, but on the re-definition of the target-word. Likewise, conflating FDB and FH3 with FH involves an incidental mathematical adjustment. Nothing more. Once linguistic conflation of separate diseases is understood, and the constituents itemized, the “higher prevalence” is exposed as a false claim. See forensic slide on page 6 and full analysis on page 14.

2. Whites of European descent are targeted in both Danish studies and the Regeneron-funded, USA-based study. Descendants from Central and Northern Europe have a higher prevalence of FDB-as-R3500Q than those whose ancestors are outside of these regions. Also, later pharma-funded reports cite a study from The Netherlands.83 The Netherlands has been reported to be influenced by founder effect, and likewise, the US-based Regeneron study includes a region with the highest FDB-as-R3500Q founder effect in the world. Founder effect should have invalidated both of these results. Just as we have gerrymandering in politics, we have “geno-mandering” in prevalence studies. See forensic slide on page 7 and full analysis on page 24.

3. **Inflated groups skew the results.** In the 1st Danish report and in the Regeneron report, standards of diagnosis are lowered. Using the recommended clinical scoring system inflates the count with false positives. Also, in the 1st Danish report, under the table, a cutoff of 5 was used in the calculation, while “6” was printed in the text. See full analysis on page 29.

4. The authors **goosed the denominator** of a key metric, which inflated the outcome. They also cherry-picked the most aggressive of 3 available ratios. After correcting the math and the linguistic conflation mentioned above, FH prevalence is actually lower than established estimates. See full analysis on page 38.

5. The results of clinical scoring systems are inherently skewed by a selection bias. A clinical scoring system such as the Dutch Lipid Clinic Network criteria is not in itself sufficient to determine FH mutation carriers. However, it is the inherited cultural assumption, and while FH is as yet unknown, big pharma is stepping in with these angled research papers to instruct toward

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83 Authors on the Netherlands’ study received money from Amgen, Regeneron, Aegerion, and others. See page 134.
clinical diagnosis, while using genetic testing, not to raise the alarm of the false positives inherent in the scoring systems, but to simply sound the alarm ... to get everyone moving along with their unchallenged, culturally inherited assumptions. It is this inadequacy of clinical screening that pharma needs to stay in place. Whenever the molecular/genetic basis of FH is merely the message, while clinical scoring systems are recommended practice, patients are swapped. This is because the majority of mutation carriers are below clinical detection while the majority of those above clinical detection are not mutation carriers. The former are difficult and expensive to find; the latter, easy and profitable. Genuine FH are swapped out and false positives, swapped in. Inadequate distinction is a passageway to larger profits. It’s a publication strategy, and it’s working. See forensic slide page 10 and full analysis on page 56.

The Regeneron-funded paper further reveals the publication strategy already evident in the 1st and 2nd Danish reports. Pharma’s funding has been influencing the medical community for several years now, the results of which are off-label sales through the redefinition of what constitutes FH. Most of these patients are not HeFH LDLR carriers (nor HoFH). They are false positives, and the one’s left behind were the real carriers. The pharma-funded publications are designed to maximize profit from this misunderstanding.
Red Flags

Citation Kiting: The industry’s “Authoritative” prevalence has no external, contemporary source.

Dr. Kay Dickersin was the expert witness in the Pfizer/Parke-Davis affair. She detailed work on an organized “publication strategy” and the resulting exploitation of biases in published scientific papers. “Citation bias” was one of the abuses exposed in her report: selecting only favorable citations and neglecting the unfavorable, previously published works. What we have with the FH publication strategy however is over-the-top. I call it “Citation Kiting.”

Bankers are on the alert for a crime called, “Check Kiting.” It takes advantage of the lag between the writing of a check and the final transfer of funds from the bank. So if a real or fake check for $10,000 is deposited into Bank A, another check for $10,000 can instantly be written against Bank A and deposited into Bank B. During the time it takes for both checks to clear, the total of printed balances would be $20,000. Now, our fraudster can show a third party “proof” of $20,000 in assets. The scheme can involve many banks or other financial institutions, until eventually he comes across a bank with lax policies or personnel who break with policy. Or perhaps he can find someone who will lend him cash against his inflated bank statement. He can even use the increasing balance of a target bank as “proof” of increasing revenue. Fortunately, there is a clearance mechanism in place for bank checks, forcing the fraudster to accelerate his pace as his balances swell, leaving it only a matter of time and a little research before this financial epidemic ends.

But what if there were no clearing house for bank checks? How absurd would that be? And yet there is no clearance mechanism for the debt one science report owes to another. A similar “kiting” scam can happen within the hallowed corridors of science. Here is an excerpt from Novelion’s latest 10-K. (Emphasis mine.)

“Medical literature has historically reported the prevalence rate of HoFH as one person in a million, based on an estimated prevalence rate for HeFH of one person in 500. Analysis of HoFH prevalence have been evolving in recent years cumulating in published medical literature that suggests that the actual prevalence of both HeFH and HoFH may be significantly higher than the historical estimate of one person in a million. For example, in 2014, the European Atherosclerosis Society (EAS) Consensus Panel on Familial Hypercholesterolaemia (FH) published an article citing research that would result in an estimate of the prevalence of HoFH in the range of between one person in 300,000 and one person in 160,000 or 3.33 persons per million to 6.25 persons per million, which is consistent with estimates that can be derived from other publications from the last few years. The FDA cited this estimate in its review of PCSK9 inhibitor products in June 2015.” ~ (emphasis mine) Novelion (acquired Aegerion) 2016 10-K

What concerns us here is the citation trail. The EAS paper cited by Novelion in the above did no prevalence study of its own. It cites another “Authoritative” report, which also did no prevalence study of its own. This Authoritative report did not even use the results of the study it cited. Consequently, there was no external, contemporary source in this Authoritative report for the new result and new criteria. The only source to the corrected prevalence rate is a self-citation within this very, selfsame, Authoritative report, found in a caption to an illustration, referring to a “personal communication” with the lead author: Borge Nordestgaard. Did someone actually talk to him? ... or did he simply talk to himself?

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84 Expert witness in Prizer trial: “Reporting and other biases in studies of Neurontin for migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain,” Dr. Kay Dickersin, MA, PhD,August 10, 2008
85 https://www.sec.gov/Archives/edgar/data/827809/000082780917000012/nvln-12312016x10k.htm#sD4A2BC7F37462D6C63C6481CE7873D5C
86 See page 116 for a list of key reports, including the “Authoritative” report.
Big Pharma had already paid honoraria to two members of the team: Nordestgaard and Watts.

2011

Kusters, Defesche, et al – a study of FH “Founder Effect” in The Netherlands. (Founder effect is an anomaly and thus Dutch prevalence cannot be representative of US Prevalence. Kusters and Defesche were also authors listed on the Sjouke report (below). Defesche is also listed on the Nordestgaard report (below). This report is not mentioned in the important prevalence report on The Netherlands by Sjouke, et al.)

2012 “1st Report”

The 1st Report concludes an FH prevalence of 1:137. (My analysis shows mathematically that genuine mutation carriers were swapped out, and false positives swapped in.)

2013 “Authoritative report”

The “Authoritative” report cites the 1st Report as the source for prevalence while using a different result and different criteria. In fact, the only contemporary source for the correction to 1:200 is a self-citation of a personal communication with the lead selfsame author found in a caption to an illustration in the selfsame report. Funded by pharma.

02/2014

Sjouke, Kusters, Defesche, et al, cite Benn’s 1st report prevalence of 1:137. This is a molecular study of The Netherlands, results – 1:244. No mention of Kusters’ and Defesche’s report on founder effect in the Netherlands, even though Defesche and Kusters worked on both reports. (This report exposes the “surprising” fact that most mutation carriers score below clinical detection. This is an essential premise supporting my conclusion that genuine mutation carriers are swapped out, and false positives are swapped in.) Many authors have received funding, fees, and honoraria from pharma.

07/2014

Cuchel, Nordestgaard, et al, cite, not the result-producing 1st report, but the “Authoritative” report, whose prevalence material was supposed to have been taken from this 1st report. But because the Authoritative report uses a different result and different criteria, the only substance to Cuchel’s citation is a personal communication mentioned in an illustration caption. (This 2014 report by Cuchel is the study mentioned in the Novelion citation on the preceding page, which mentions the FDA’s citation, as support of prevalence.) Cuchel also has a citation to the Sjouke Dutch study (above), a population influenced by founder effect. Funding and honoraria by pharma.

12/2014 “Corrigendum”

Finally, the “correction” to the 1st report arrives – the Corrigendum – adjusting the criteria used and stating that the 2012 1st report results should have been 1:223. This is the only external source for the doubling of prevalence in the report regarded as “authoritative” in the industry and among regulators. This source for the now doubled FH prevalence arrives – as if in a time machine -- after these numbers had already been accepted by the industry.

2016 “2nd Report”

The 2nd report’s prevalence is said to be “comparable” to the 1st report’s (presumably the Corrigendum’s). We learn here that the top 4 most frequent mutations which originally scored above the clinical detection point in the 1st report could not possibly have exceeded 25. Using deduction while reconciling these two reports, it is a mathematical certainty that genuine mutation carriers were swapped out and non-mutation carriers swapped in, from one report’s procedure to the other’s. They are largely different populations, and so the proximity in their prevalence rates is a coincidence and not a confirmation. (See page 62) Citations throughout the industry and even within the FDA, refer to the Authoritative report and not back to the source and its methodology!
There was no external, contemporary source in this Authoritative report for the new result and new criteria.


- Only support for new result and new criteria is a personal communication with Nordestgaard, lead author.
- Caption to illustration citing Personal communication
- Left: Cuchel citation to Nordestgaard can only be to caption.
- Right: Cuchel cites Sjouke’s, Kusters’, & Defesche’s research, which does not cite Kusters’ and Defesche’s earlier work.
- Academia cites Cuchel’s report and Nordestgaard’s report, both mere citations of a personal communication.
- FDA and insurance companies take prevailing academic inertia as “authoritative” and cite Cuchel’s and Nordestgaard’s papers, as if sources of authoritative conclusions.
- Novelion/Aegerion proves its claim of prevalence by citing ... the FDA’s use of ... a citation of a personal communication.
- Big Pharma Profits are estimated to be in the billions. Aegerion’s market cap alone soars to over $2 billion.

Either/Or predicament not mentioned

Either: Dutch = USA
- 2014 S, K & D
- Dutch = USA
- 2011 K & D

If this work holds, then Dutch prevalence cannot apply to the USA. S, K, & D’s 2014 conclusion of USA relevance fails, and with it, Cuchel’s citation fails.

Either: Dutch ≠ USA
- 2014 S, K & D
- Dutch ≠ USA & Cuchel

If this work holds, then K & D’s 2011 conclusion of extraordinary circumstances in The Netherlands should receive some explanation or retraction.

2011 K & D
- Dutch ≠ USA

100

Results and criteria do not match
There is no “citation clearing house” – even when human health and billions of dollars are at stake. The 1st report has vanished from concern ... the source. Below, we can see the first step in the removal of the prevalence conclusion from its own source.

From here on the Authoritative report is cited in the industry as if it were the source material itself. As of November 2016, Google Scholar lists 583 citations.87

This is a multibillion-dollar industry. And the new prevalence and new criteria rests on a personal communication, with the selfsame lead author? There is no external, contemporary source for the correct prevalence result.

Here is a circumstantial but scary thought: Dr. Peter Gotzsche of the Nordic Cochrane Centre wrote a report on ghost authorship in Danish scientific research, having found that 75% of randomized trials over a 2 year period involved ghost writers.88 Who consulted with Dr. Nordestgaard? Again, this is only a circumstantial juxtaposition of facts, so caution is warranted. But here is Dr. Peter Gotzsche again,

*It is still commonly accepted that department chairs claim authorship of all papers emanating from the department, and newspaper articles celebrating a professor's 60th birthday may note...*

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87 https://scholar.google.com/scholar?as_sdt=1,48&hl=en&scid=0,48&cites=5902718471118150349&scisig=

88 “Ghost Authorship in Industry-Initiated Randomised Trials”
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0040019
that he or she has written more than 500 papers. The professor may have contributed, but almost certainly wrote only a minority of them.\textsuperscript{89}

It is a perfect game. If all goes well, the professor simply says nothing and absorbs all the prestige. If it goes badly, he simply says, “It wasn’t really me.” Now, I can’t say that Dr. Nordestgaard simply hired out his name and that ghost writers have done much of his work. I can say that the University of Copenhagen credits him with 438 scientific publications.\textsuperscript{90} For the last couple of years he has been averaging about 1 per week.

But here is another circumstantial fact which may or may not have place in this jigsaw puzzle: Dr. Adriane Fugh-Berman, who was expert witness in the Wyeth trial, helped expose the widespread practice of ghost writing in medical literature. Here is the first summary point of her paper, “The Haunting of Medical Journals: How Ghostwriting Sold ‘HRT’”:

> “Some 1500 documents revealed in litigation provide unprecedented insights into how pharmaceutical companies promote drugs, including the use of vendors to produce ghostwritten manuscripts and place them into medical journals.”\textsuperscript{91}

The new prevalence count in the Authoritative report has no external, contemporary source. And yet now the medical community is reporting that there is a higher prevalence than previously thought and it is this Authoritative report, itself, that is widely cited as if the actual source of the “discovery.” But that would mean that the industry accepted an obscure comment in the caption to an illustration which doubled the prevalence of a serious disease, doubling also the addressable market for a multibillion dollar industry ... without blinking.

Other facts can be blinked out of the source material. The studies in Denmark were of whites of Danish descent. At the end of successive research papers this restricted population was eventually declared to be a study of the “general population.” Here’s how the same study of “whites of Danish descent” becomes a study of the “general population.”

Only Benn, et al, performed a prevalence study. The following two reports simply cited Benn. Cuchel, by citing

\textsuperscript{89} “What Should Be Done To Tackle Ghostwriting in the Medical Literature?”, Peter C Gøtzsche, Et al, http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000023
\textsuperscript{90} http://research.ku.dk/search/?pure=en%2Fpersons%2Fboerge-nordestgaard[733103b5-ddc2-416f-a686-48e694154a82]%2Fpublications.html
\textsuperscript{91} http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000335
Nordestgaard and not the original, can take Nordestgaard’s statement of “general population” and omit mention of Benn’s, original disclosure of “all whites of Danish descent.” Now as if representative of the USA, we move from a very specific slice of demographics, to something which represents all of the USA, with one and the same source population: whites of Danish descent. These studies were funded by Big Pharma players and were promoted in the USA. Nordestgaard’s and Cuchel’s papers have been highly influential, and have been cited by the FDA. And then in the next step, the FDA is cited by Novelion (formerly, Aegerion) to add credibility. A full circle is completed. Pharma punches in the very information and credibility it needs to pull back out. (The emphasis is mine.)

“... in 2014, the European Atherosclerosis Society (EAS) Consensus Panel on Familial Hypercholesterolaemia (FH) published an article citing research that would result in an estimate of the prevalence of HoFH in the range of between one person in 300,000 and one person in 160,000 or 3.33 persons per million to 6.25 persons per million, which is consistent with estimates that can be derived from other publications from the last few years. The FDA cited this estimate in its review of PCSK9 inhibitor products in June 2015.” ~ Novelion Therapeutics Inc., Dec. 2016 10-K😄

Now for the industry, and even the FDA, the original source material has virtually disappeared. Real money has been lent, borrowed and invested based on these reports and subsequent citations of them. But there’s more. I will demonstrate mathematically in the second half of my analysis that the actual source for the above swapped out genuine mutation carriers and swapped in false positives. These false positives have been prescribed risky, new drugs. This is citation kiting: the industry draws credibility from an FDA citation, which drew credibility from the Authoritative report and yet the Authoritative report is an empty account drawn against an original empty account. They may even be ghosts which are “writing checks,” as it were, against this original phantom balance. Who can know?

- Question: Why does the industry cite the Authoritative report and not the Corrigendum to the 1st Report?
- Answer: The 1st Report was clearly manipulated. See pages 14, 24, 29, 30, and 69.

It is a simple mechanism, like a rudder to a ship: citation kiting steers the phantom “source” cited by the industry away from the genuine source.

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92 https://www.sec.gov/Archives/edgar/data/827809/000082780917000012/nvln-12312016x10k.htm
Conflict of interest in the 2nd report?

In the 2nd report, this is supposed to be a mention of financial interests.

Just a couple months earlier, Nordestgaard had been publicly accused of being financially tainted by the industry.

“A major row has erupted over conflict of interest claims involving a study linking negative news stories about statins with an increased risk of heart attacks and death. One of the study’s two authors, Danish scientist Professor Borge Nordestgaard, has admitted receiving consultancy fees and lecture payments from a host of drug companies.”

And in his rebuttal he seems to think that he does not need to disclose financial interests any longer.

“Prof Nordestgaard refuted any suggestion of bias, and pointed out that most statins were now off-patent and made by generic medicine companies that he had “nothing to do with”. He told the Press Association: "I might as well have written that I had no conflict of interest."

And now here we are, a couple months later, with the above entry for “conflict of interest.”

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94 Ibid.
Copenhagen Study Population Confusion.

Is the population of the study 98,098, 98,000, or 99,098?

Although the title to the report says that there were 98,098, the actual constituents of the population were not rounded and they totaled exactly 98,000. Nonetheless, it is clear that the authors used 98,098 for the “Results.” The first APOB prevalence step makes this clear: 98,098÷111=883.77, which rounds to 884 – the authors’ result. Whereas using 98,000 comes out to 882.88. The difference is also illustrated with the first step in LDLR calculation, 1557 versus 1555.56. (98,098÷63=1557 and 98,000÷63=1556.) It is clear that in the results, 98,098 was used. However, it is equally clear that the unrounded constituents of this population add up to 98,000 exactly.

Here is a screenshot of Table 1 in the 2nd report.

Another problem: in the section, “Methods,” we have yet another number. 99,372 minus 274, equals 99,098 and not 98,098. The population size here is 1,000 off of the title’s population.

And there are more problems: See also the next page for a screenshot of Table 5, of the 2nd report’s Supplement, with my commentary.
Note that all three categories have a way of adding up to 98,000; the 1st, only when limited to the final column: its first row doesn’t add up. The 2nd is consistent in both rows and columns, totaling 98,000. The last, “Make Early Diagnosis,” adds up to 98,000 ... until we get to the final column. The total is off by 4,602, yet this total was used in the 2nd report within Table 1. And not to forget, in addition to being in the title of the report, 98,098 was clearly used for the study’s “Results.” Whatever the population total was supposed to be, the cells within this table are internally inconsistent.

### Supplementary Table 5.

Participants in the Copenhagen General Population Study categorized by the Dutch Lipid Clinic Network criteria, the Simon Broome criteria, and the Make Early Diagnosis to Prevent Early Death criteria, ignoring information on mutation carrier status during categorization, but subsequently reported by mutation carrier status.

<table>
<thead>
<tr>
<th></th>
<th>LDLR or APOB mutation (n=174)</th>
<th>LDLR mutation (n=63)</th>
<th>APOB mutation (n=111)</th>
<th>Non-carriers (n=97,924)</th>
<th>All (n=98,098)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Lipid Clinic Network criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely, n (%)</td>
<td>66 (38%)</td>
<td>21 (33%)</td>
<td>45 (41%)</td>
<td>90,000 (93%)</td>
<td>90,956 (93%)</td>
</tr>
<tr>
<td>Possible, n (%)</td>
<td>83 (48%)</td>
<td>23 (37%)</td>
<td>60 (54%)</td>
<td>6,620 (6.8%)</td>
<td>6,703 (6.8%)</td>
</tr>
<tr>
<td>Probable, n (%)</td>
<td>19 (11%)</td>
<td>13 (21%)</td>
<td>6 (5.4%)</td>
<td>297 (0.3%)</td>
<td>316 (0.3%)</td>
</tr>
<tr>
<td>Definite, n (%)</td>
<td>6 (3.5%)</td>
<td>6 (9.5%)</td>
<td>0 (0%)</td>
<td>19 (0.2%)</td>
<td>25 (0.03%)</td>
</tr>
<tr>
<td>Simon Broome criteria</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unlikely, n (%)</td>
<td>84 (48%)</td>
<td>23 (37%)</td>
<td>61 (55%)</td>
<td>94,011 (96%)</td>
<td>94,095 (96%)</td>
</tr>
<tr>
<td>Possible, n (%)</td>
<td>90 (52%)</td>
<td>40 (63%)</td>
<td>50 (45%)</td>
<td>3,815 (3.9%)</td>
<td>3,905 (4.0%)</td>
</tr>
<tr>
<td>Definite, n (%)*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Make Early Diagnosis to Prevent Early Death criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely, n (%)</td>
<td>134 (77%)</td>
<td>10 (13%)</td>
<td>94 (85%)</td>
<td>97,077 (94%)</td>
<td>92,609 (94%)</td>
</tr>
<tr>
<td>Probable, n (%)</td>
<td>40 (23%)</td>
<td>23 (35%)</td>
<td>17 (15%)</td>
<td>749 (0.8%)</td>
<td>789 (0.8%)</td>
</tr>
</tbody>
</table>

*A definite diagnosis of familial hypercholesterolemia requires information on mutation carrier status or presence of tendon xanthoma, and as we did not have information on tendon xanthoma in the present study, and as information on mutation carrier status was on purpose not used in
Observations

Contingency table exposes the motive & 78% false positives

We see the reasons why the molecular results in the 1st report were not revealed alongside their original clinical scores. In a real-world, clinical situation the 1st report’s ADH population would be made up of 78% false positives (without margin for error, estimated 80.5%, see page 73). In the illustration below, we see our breakdown of the clinical results above and below the detection point, further separated into those determined to be either mutation carriers or non-carriers. Simply put, big pharma cherry-picks authors and funds their Authoritative report. This is tantamount to promoting off-label, but the two supporting reports must be reconciled to see this. Big pharma has engineered a social condition, the outcome of which will be off-label prescriptions and a gross exaggeration of the addressable market.

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95 On “Cherry-picking” scientists, see page 113.
Smoothly off-Label: The Trick to the 1st report is the basis for the Authoritative report

The 1st report was designed to take advantage of the overlap between phenotype and genotype – those who clinically look like they might have the disease as opposed to those with a confirmed mutation. They went one step further. They took all of the clinical and then after neglecting to use molecular results to gauge accuracy, simply added in the molecular hits. They get the best of both worlds.

Add both and get the best of both worlds.

Choose all clinical results in the top 2 DLCN categories.

Looks Like FH and tested positive for one of the Top4 mutations. Accurate & accessible

Join

Looks like FH and so it is deemed FH. Devalues the question of false positives. Easy market & Largely Inaccurate

Join

Doesn’t look like FH but Top4 mutations were found in this academic study. Give these a passing clinical score and send them to the patient pool above. The other mutation carriers, a majority in the aggregate, are left unaccounted for.

Difficult & Unprofitable

More will be deemed FH through a clinical scoring system than with molecular confirmation – by the same principle that there will be more criminal suspects with circumstantial evidence than with forensic confirmation.

It is difficult, time consuming and expensive to test everyone. Although it can serve an academic and promotional purpose, genotyping 60,000 from the general population is not practical.

The authors opted to hide this breakdown of their molecular hits under a crude total, creating the illusion of a target-rich patient pool. But how does one hide the original molecular breakdown into clinical categories ... after molecularly screening 60,000 people?

Epistemological demotion -- rename the genotyped to “Phenotype.” Strikingly, for the 1st report, molecular results were gathered from about 60,000 Copenhagen residents. Despite this large emphasis on molecular detection, the study nonetheless focused on the clinical: the genotyped are actually demoted epistemologically and lumped together with the phenotyped. To use a legal analogy, this would be like putting in the work and finding forensic evidence but then reclassifying and presenting it to the jury and judge as “even more circumstantial evidence than previously thought.” This would only make sense if one either did not understand the superiority of forensic evidence or understood and therefore found no profit in the forensic conclusion.
Of course, accepting all mutation carriers below the clinical detection point makes sense. One wants to be sure that all ADH are accounted for. The clinic would retrieve false negatives, without pulling in more false positives. But then again, this epistemological demotion does not make sense. In a professional prevalence study, such as the reports we are currently analyzing, it makes more sense to use the molecular to gauge the accuracy of the clinical. We want to know how many false positives there are. How accurate are we? What we have instead is a preference for inaccuracy, because the genotypic would expose and the phenotypic would conceal the false positives. Now we can append the 100% accurate molecular to the inaccurate clinical. We dodge the standard discipline of putting our results into a contingency table. Inclusion criteria increases profit, and exclusion criteria decreases profit, because the former increases errors and the latter increases accuracy. In an academic study, who would do this and why? Who is interested in blending the phenotypic in with the genotypic to arrive at a larger number, by lowering accuracy? Here is the previous illustration with some quotes from the Authoritative report. It follows, in text, the method from its source for the results: the 1st report.
**Gold Standard:** What is missing from the 1st and Authoritative reports is a concern for false positives ... a crosscheck of the clinical procedure with the gold standard: molecular testing.

“The gold standard of diagnosis is the identification of the underlying genetic defect, which is possible in 80% of cases and enables the identification of affected relatives of the index patient.”

Not so, for the industry. Their Gold Standard is financial gain, not diagnostic accuracy. It is more profitable to discourage the molecular and emphasize the clinical. Those who look like mutation carriers will significantly outnumber actual mutation carriers. In the 1st and Authoritative reports, “FH” patients are only the default of the discouraged molecular approach. This error-harvest will make up for the inaccessibility and irrelevance of many of the actual mutation carriers. To the degree that the medical community can be persuaded to regard this clinical approach as the “gold standard,” the clinical setting effectively renames these errors as “True Positives.” This is significant, not in small part because it so subtle. **Here’s how the industry can change the indication without FDA approval:** shift from the more accurate genotype to the less accurate phenotype. Any legitimacy given to lowering standards will effectively rename “off-label” to “on-label.”

1. Scope of the problem: FH is underdiagnosed

Before the publication of this Consensus Statement, it was generally accepted that about one in 500 people in the general population have heterozygous FH, and one in a million have homozygous FH [3]. However, these values have been questioned as they were derived from clinical data from over 30 years ago, using less accurate methods.

Indeed, recent data from the Copenhagen General Population Study, an unselected North European general population sample, highlight that these values markedly underestimate the prevalence of FH. Based on the Dutch Lipid Clinic Network criteria for FH (regarded as the gold standard), it was estimated that about one in 200 people had definite or probable FH [4]. These estimates therefore suggest that up to 34 million people may be affected by FH worldwide (Fig. 1).

Also, one need [sic] to consider that what mainly causes ASCVD in FH is the severely elevated LDL-C and not the genetic defects. Therefore, the phenotype is more important in the clinician’s point of view to identify and treat FH. This is clearly seen here in the study of Raal et al where there was variability on the HoFH phenotype.

....

To conclude HoFH is still a devastating disease with a huge burden of ASCVD and early mortality risk, however it is more frequent and heterogeneous than we once thought. Recognizing this heterogeneity and the overlap with HeFH is important for clinical

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96 Familial Hypercholesterolemia: Developments in Diagnosis and Treatment; Gerald Klose, Ulrich Laufs, Winfried März, Eberhard Windler; 2014
management. **Phenotype and not the genotype should be the physicians’ main concern**, and **those with most severe phenotype have to be more aggressively treated**. Unfortunately FH as a whole is **still underdiagnosed and undertreated** and many opportunities to save lives are being lost.

**Acknowledgments:** RDS has received honoraria for consulting/speaker activities from: Astra Zeneca, Amgen, Aegerion, Akcea, Biolab, Boeringher-Ingelheim, Cerenis, Genzyme, Kowa, Pfizer, Sanofi/Regeneron, Unilever and Torrent.98

Ironically, the “FH” population is indeed “underdiagnosed.” Here is a different perspective, from Fahed and Nemer. In sum, clinical screening is not the efficient way to find mutations carriers.

“FH is a disease that shows great phenotypic variability.” .... “Due to the paucity of data on genotype phenotype correlations, clinical diagnosis will miss a large percentage of FH patients. It is currently estimated that only 15 to 20% of patients with FH are actually diagnosed. A study on 643 Danish probands could not even find a single phenotypic characteristic to predict the existence of a mutation.”99

**Problem:** So “FH” is indeed underdiagnosed. There will be underdiagnoses ... because Clinical testing is not going to find the majority of mutation carriers, and this is because most mutation carriers are below the clinical detection point. The authors’ own 2nd report shows this. And the predominant clinical solution recommended in the Authoritative report is the cause of molecular underdiagnoses.

The reason why molecular screening doesn’t work for the industry is because finding all of these mutation carriers is difficult and unprofitable:

- Because the majority of mutation carriers score below the clinical detection point, real-world clinics are not going to flag most of them, and thus entire populations would need to be screened for this group to become medically relevant. This is not a profitable strategy.

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98 Homozygous Familial Hypercholesterolemia: phenotype rules! Commentary on the study of Raal et al. Raul D. Santos Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital and Preventive Medicine Centre and Cardiology Program Hospital Israelita Albert Einstein, Sao Paulo, Brazil. Atherosclerosis. 2016 May; 248:252-4. doi: 10.1016/j.atherosclerosis.2016.03.015

99 Familial Hypercholesterolemia: The Lipids or the Genes? Akl C Fahed and Georges M Nemer; 2011
• And even of those above the clinical detection point, a significant portion will not be found to contain a mutation. Tightening the standards improves the hit rate as a percentage, but of course this requires that one accept a smaller pool of candidates. This avenue is simply not profitable.

• However, even if molecular screening were used, many mutation carriers would still be below the cutoff point. Studies show that many have compensating genes, sufficiently good environmental factors, or one of the milder mutations – and consequently, many in this false negative category may not require expensive, specialized medication. This is not profitable.

It’s a big problem when medical relevance is financially irrelevant ... and a powerful force on behavior: tapping a mere clinical procedure will inflate the patient pool with quick and easy to acquire false positives. The industry can then simply add in the molecular results, instead of using them to gauge accuracy.

Solution: It is more profitable to steer the medical and investing communities away from genetic testing than toward it ... while also trying to convince everyone that environmental solutions do not work well with such a genetically inherited disease. A molecular danger scares up a clinical profit. Tough sell. But that’s what’s happening. Treating the false positives with FH drugs is easy if you convince the medical community to stop short of molecular confirmation. It finds many more of those suffering from environmental factors than it will find carriers of LDLR mutations. Pharma admits that there are too many false negatives, but then uses that admission to neglect most false negatives and thus secure more false positives. It is financially rational; humanly insane.

This neglect of the true mutation carriers below clinical detection is deliberately engineered by the industry. The Authoritative report is a large factor in this effort. Molecular testing is just too expensive and reveals the majority of carriers to be below the detection point. The solution? Broadcast the fact that patients are indeed overlooked in order to elicit sympathy toward securing more clinically determined patients, thus making up for the deficit of on-target patients by prescribing the drugs to larger numbers of off-target patients. In the end, money twists health values into a logic-pretzel -- like sending flood relief to Bakersfield because New Orleans is inconveniently underwater, and then validating this with the fact that the two cities’ populations just happen to be roughly the same.

Deceptive “comparison” of populations: The irony is that the mutation prevalence rate in the 2nd report is very close to the 1st report’s clinical prevalence. So why not emphasize the more forensic of the two approaches? ... the molecular? Why use the molecular to promote the clinical?

Besides the reasons already discussed, there is another reason for the molecular emphasis in the 2nd report. If the totals of the prevalence counts in two reports are seen as “comparable,’ then 2 mice over here can confirm that there are 2 elephants over there. This will not be so conspicuous, if the average
reader is unfamiliar with the terms and definitions in question: two distinct constituents of a total will be given extra cognitive room within which to be “compared.” With the clinical process, a tomato at a distance of 20 yards can look like a red apple and I can then write down on paper, “It looks like there are 2 apples over there.” That statement is all that the reader sees. And I can later subject a red apple and a green apple to the more forensic taste test and then write that I once again have a total of “2” and now because this total “2” is truly comparable to the previous total “2,” that tomato is now an apple, on paper. Of course, reconciling the forensic approach with the weaker report would render this deception conspicuous. So we do want the forensic report, but only so much as it exists to recommend the weaker report and no more.

**Scienter:** The proximity of the totals of the two reports can appear, from one perspective, to be only a coincidence. But then again, this falsehood has to be deliberate. The authors are experts in their field, they are not unsophisticated, and they knew that the majority of mutation carriers originally scored below the clinical detection point. The authors had this same raw data in the 1st report – since it makes up almost 60% of the population of the 2nd report. They could not have completed either report without this knowledge. From that perspective, the similarity in the prevalence numbers is not just a coincidence; it plays a necessary role in the deception.

**The Larger Issue: Pharma “cherry-picks” researchers, corrupting scientific procedure**

To the degree that the medical community and public opinion can be bent toward Wall Street interests, it will be academic corruption not contagion itself that spreads ill-health on a vast scale.

Scientists receiving Honoraria from Pharma are gaming scientific procedure to tilt data toward financial prospects. When Wall Street out-funds a full scientific debate, permitting only the profitable side of the debate to reach the audience, everyone loses. By “cherry-picking” those few scientists whose independent views represent Pharma’s own financial interests, and leaving alternative yet widely held views unfunded and unheard, Pharma can engineer a social condition toward its own profit, and fool many observers into thinking that an “independent view” is not actually dependent upon special lighting and exclusion. It is not only Aegerion, but others in the FH space, which made these papers possible and influential. The financial interests in developing opinions which loosen standards for diagnosis, and thus increase diagnostic false-positives, parallel with an increase in the “addressable market.”

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<tr>
<td>Funding</td>
<td>Funding</td>
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<tr>
<td>Supported by unrestricted educational grants to EAS from Amgen, Aegerion, AstraZeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron. These companies were not present at the Consensus Panel meetings, had no role in the design or content of the Consensus Statement, and had no right to approve or disapprove the final document.</td>
<td>The European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia is supported by unrestricted educational grants from Amgen, Aegerion, AstraZeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron. These companies were not present at the Consensus Panel meetings, had no role in the design or content of the manuscript, and had no right to approve or disapprove the final document. Funding to pay the Open Access publication charges for this article was provided by the European Atherosclerosis Society.</td>
</tr>
</tbody>
</table>
The notion of an “independent”... “consensus statement” is meaningless. For example, I could “cherry-pick” only those who have previously supported the notion that the earth is flat and fund only those who would in turn select only “team players” that would condone the use of manipulated procedure. I would thus, enable the greater reach of my own point of view, completely ignoring contrary reviews, and then claim this to be a “consensus statement” of independently held views. In reality, I would be carefully bringing to my audience only those whose already-declared, independent opinions were already in my own interests. My activity in engineering the conclusion is out of view, since it precedes the presentation, and my passivity is in full view, as already-existing opinions need no push or coaxing. For example, I could specifically select only those Australian witnesses who have independently left affidavits swearing that while in Australia they were not hanging upside down by their ankles. Assembling this data into a research paper, even though they received funding from myself, I could state boldly and honestly that ...

I was not present at the Consensus Panel meetings, had no role in the design or content of the Consensus Statement that Earth is flat, and had no right to approve or disapprove the final document.

Also note that the data subject to the 2013 EAS “consensus” is derived from a single, specific study of “whites of Danish descent” and, as demonstrated in this report, that data was derived after manipulating and lowering the standards of the criteria for diagnosis. But a “consensus” of cherry-picked opinions is a stronger bias. It is truly “independent” ... of alternative and opposing opinions. Since Karl Popper, it is to be understood that what is built on confirmation is brittle, but that which survives attempts at falsification is robust. “Consensus” is not scientific evidence or a goal, but a red flag.

The “consensus panel” in the EAS papers did not include contrary opinions such Van der Graaf and Van Aalst-Cohen and others, whose work revealed a completely neglected point of view ... even though Van Aalst-Cohen’s and Van der Graaf’s research was published before the EAS papers.

Aegerion, and pharma, simply fail to give account to existing contrary opinions, leaving them unfunded, unquoted, and unreferenced. Thus although Aegerion’s promotion appears to be indirect, and although scientists may actually be reaching their own independent conclusions, pharma has engineered a condition the result of which is direct control over the message conveyed to the public and medical community.

For example, when Aegerion is trying to convince Europe of the rarity of the disease, in order to quality as an “orphan drug” and thereby receive special treatment in the approval process, it funds on-the-ground research which results in a 1:800,000 HoFH prevalence rate – very close to the number held by scientists at large. However, when Aegerion is addressing its profitability, it tries to convince investors

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100 Such affidavits evidently actually exist. ["Marjory has always known that the earth is flat, too," says Charles Johnson. "As far as she knew, everybody in Australia knew it. She was rather shocked when she arrived here and found people speaking of Australia as being 'down under.' It really offended her. She would get in quite heated arguments with people who seemed to accuse her of coming from down under the world." Ultimately, Marjory Johnson swore in an affidavit that she had never hung by her feet in Australia.] Article in 1980 by Robert J. Schadewald; The Flat-out Truth: Earth Orbits? Moon Landings? A Fraud! Says This Prophet https://www.lhup.edu/~dsimanek(fe-scidi.htm

114
and the medical community that there are far more patients than the scientific community thinks. It sets aside its own recently used study, does not mention it again, and joins in the funding of a specific, shoddy Danish study, one whose standards for deciding who is an FH patient have been lowered substantially. The difference between scientist’s earlier estimates, to regulators, and later estimates, to investors and doctors, is a staggering 1,000%. Both sets of scientists reached their own “independent” conclusions – both funded by Aegerion.

Scientific culture precedes science

Science in America is still in a life and death struggle with its own culture. As a publication strategy, the aim and function of the Authoritative report is to keep clinical diagnosis on the table alongside the more rigorous molecular approach. Clinical testing must not be presented as one of two steps toward definitive confirmation, but clinical testing must be regarded, in itself, as sufficient for identifying FH. It is a publication strategy which not only omits new discoveries but actively pushes the prevailing cultural error all the way through drug testing and FDA approval. Clinical testing for this genetically inherited disease is now taken for granted as the “gold standard,” not genetic testing. As a consequence of this cultural success, real mutation carriers are swapped out of the patient pool, and non-mutation carriers are swapped in.

And the irony is that “FH” is indeed underdiagnosed. There will be underdiagnoses ... because Clinical testing is not going to find the majority of mutation carriers, and this is because most mutation carriers are below the clinical detection point. The authors’ own 2nd report shows this. And the predominant clinical solution recommended in the Authoritative report is the cause of molecular underdiagnoses.

The pharma industry has funded and promoted a social condition whose strategic outcome is an increased error-rate in diagnosis, resulting in an increased number of off-label prescriptions. It effectively renames the FDA indication for “FH” drugs. This also inflates the addressable market and misrepresents the source of revenue.

“This prevalence of FH is comparable to our previous report in a smaller sample of the same population based on phenotypic DLCN criteria alone.” ~ 2nd report, Benn, et al. 2016

No. False and False.

1. The unflooded Bakersfield may have a “comparable” population to the flooded New Orleans, but it would be deceitful to draw such a conclusion in the context of flood relief for the unflooded Bakersfield. Likewise, the clinical total which includes the clinically accessible false positives compares well with the molecular total which includes the clinically inaccessible false negatives, but it is deceitful to draw such a conclusion in the context of selling new and risky drugs based solely on clinical determinations. The majority treated will not have LDL-R mutations. They will be off-label.

2. 60,710 out of 69,016 from the study were genotyped. There were approximately 100 molecular hits. These genotypic hits were demoted by giving them a clinical score, and thus placing them among the phenotyped. This procedure allowed the authors to dodge a responsible showing of the original DLCN scores. What did these molecular hits look like before reassignment to the clinical? The fact that most of the mutation hits would have been impractical in a real-world, clinical setting is now rendered obscure. False Positives can successfully masquerade as True Positives, while False Negatives – the genuine mutation carriers -- are abandoned.
Appendix

Review of key scientific reports

| The “1st report” See footnote 101 | 2012: 1st report by four authors: The authors used lowered standards of diagnosis to an extreme, inflating the count with false positives. They also printed “6” in the text as the diagnostic cutoff while using 5 off-text in the actual calculation, claiming 1:137 prevalence. (The established prevalence is 1:500.) Key authors received funding from big pharma. This paper is cited in the Authoritative report (below) as the “source” for the dramatically new and improved prevalence rate. Not quite. Although this is the source for understanding the means of deriving the eventual results, it is not the source for the actual results used by Nordestgaard, et al. The results here are incorrect and only used by those unaware of the published Corrigendum (see below). During my analysis, when I refer to the 1st report in reconciliation with the 2nd report, I refer to the methodology of this 1st report, while using the criteria and results of the Corrigendum. Among at least two of the authors, collectively, money has been received from AstraZeneca, Merck, Pfizer, Abbott, Sanofi-Aventis, Roche, Amgen, Novartis, Boehringer-Ingelheim, GlaxoWellcome, Genfit, Karo Bio, Omthera, and Regeneron. This report also appended genetic results to clinical results, and did not present the breakdown of the genetic results into their original clinical scores. They then later claimed that this was a solely phenotypic result, but this was so only because the genotypic were given a phenotypic score. As we shall see, this demotion of the genotypic to the phenotypic in this 1st report obscures the existence of off-target mutations below the clinical cutoff and replaces them with false positives. |
| The “Authoritative Report” See footnote 102 | 2013: Three of the authors of the 1st report (above) join a larger team and write this “consensus report” -- funded by Big-Pharma: Amgen, Aegerion, AstraZeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron. This report is widely cited and has influenced FDA and Insurance formulary perceptions. In a caption to one of the charts in the selfsame Authoritative report, we find the key prevalence information and correction to the|
| The “Corrigendum” to the 1st report | **2014:** This is the only external, detailed accounting using the new and improved prevalence rate, and yet it is not cited in the Authoritative report. But the authors have a good excuse. It would have required a time machine. The Corrigendum did not yet exist at the time the Authoritative report was published. Its total is highly cited by regulators, investors, and the industry. But almost all cite ... the Authoritative report ... as if it were the source, even though the Authoritative report did not conduct a prevalence study of its own. The exaggerated numbers had been shouted loud and clear in the 1st report; this later Corrigendum was relatively quiet. In the correction, the authors issued an apology, moved the diagnostic standard up one notch, and still doubled the prevalence to 1:223. My analysis estimates that half of the corrected results were still made up of false positives.  

With health and billions of dollars at stake, why not insist that real sources be cited when extreme increases in prevalence are declared in FDA submitted documents? |
| The “2nd report” | **2016:** The same four authors appear to verify the prevalence of their 1st report but actually provide the greater detail that refutes it deductively. The same 60,000 people are shared between the two reports. Data from this later report provides an inside view to a constituent population used in its entirety in the 1st report and shows that even after granting the highest molecular results mathematically possible, the 1st report was, at a minimum, 51% inflated with false positives.  

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103 See “Citation Kiting” on page 98.
jcem.endojournals.org J Clin Endocrinol Metab, December 2014, 99(12):4758–4759
105 “New management, same old tricks: how the promotion of manipulated science is misrepresentation of market and off-label promotion”
106 2016: Mutations causative of familial hypercholesterolaemia: screening of 98,098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217: Marianne Benn, Gerald F. Watts, Anne Tybjærg-Hansen, and Børge G. Nordestgaard (Note, this includes the supplementary material) 2016: Supplementary Material: How to identify persons with mutations causative for familial hypercholesterolemia: Screening of 98,098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217 European Heart Journal (2016) 37, 1384–1394  
doi:10.1093/eurheartj/ehw028
real-world estimates, and considering the addressable market, the actual false positive percentage was probably closer to 80%. Reconciliation of the two reports also shows that two different constituents are passed off to the reader as if the same people, and as if the coincidental similarity in their total number proves the 1st report. From the 2nd to the 1st report, genuine mutation carriers are swapped out, and false positives, swapped in. In sum: Under careful scrutiny the 2nd report decisively refutes the 1st report, upon which the Authoritative report depends.

Red Flag: After some authors disclosed receipt of pharma-money in the 1st and Authoritative reports, the authors declare no financial interest in the 2nd report, as if they’d never been financially interested in the Big-pharma agenda.

The “Regeneron report”
See footnote 107

2016: It adds evidence to my analysis of the preceding reports and provides an outline of the whole publication strategy. (1) It repeats the linguistic conflation of separate diseases. (2) It repeats the targeting of advantageous geography, what I call, “Geno-mandering.” (3) It again inserts an inflated group into the results. (4) It continues the engineering of a social condition, the outcome of which is off-label marketing: from genetic message to recommended clinical diagnosis, genuine carriers are swapped out and false positives swapped in.

Other Significant Reports

Cuchel
See footnote 108

2014: Report promoted by Aegerion (now Novelion) in SEC filed 10-Ks. Its source for prevalence is the Authoritative report, even though the Authoritative report’s source was supposed to be the 1st report (above). It also cites the Sjouke report (below), which is a study of The Netherlands – a country whose FH population was earlier reported to be influenced by founder effect. (See Kusters report below.) Cuchel was involved in Aegerion’s Juxtapid/lomitapide studies. Funding by pharma.

Sjouke
See footnote 109

2014: Molecular study of The Netherlands. Used in Cuchel’s report (above). Even though Kusters and Defesche had already joined an earlier study (below) which concluded founder effect in The Netherlands, they join the team here which claims that the prevalence rate

can be extrapolated to the USA. The study also finds that most mutation carriers score below the clinical profile. Funding by pharma.

**Kusters**

*See footnote 110*

**2011:** An earlier study of founder effect in The Netherlands. Defesche is also one of the authors. Founder effect is an anomaly where genetically inherited diseases can have inordinately high prevalence rates. A population influenced by founder effect cannot reasonably be used as a proxy for the general population or the USA.

**The “Earlier Report”**

*See footnote 111*

**2005:** Three out of four of the same authors of the 1st and 2nd reports published an earlier report. These authors show an understanding of the variability of mutation phenotypes and the significance of environmental factors. See also page 77.

**Damgaard**


**Brusgaard**


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110 Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes; D. Meeike Kusters, Roeland Huijgen; Joep C. Defesche; Maud N. Vissers, Iris Kindt, Barbara A. Hutten and John J.P. Kastelein (2011)

111 2004: Phenotype of Heterozygotes for Low-Density Lipoprotein Receptor Mutations Identified in Different Background Populations: Anne Tybjærg-Hansen, Henrik Kjærulf Jensen, Marianne Benn, Rolf Steffensen, Gorm Jensen, Børge G. Nordestgaard *Arterioscler Thromb Vasc Biol.* is available at http://www.atvbaha.org DOI: 10.1161/01.ATV.0000149380.94984.f0
## Terms

| Deductive Ceiling | The 1st and 2nd reports involve the same 60,000 population. The 2nd report adds approximately 40,000 to that population. Of this 100,000, there were 25 molecular hits above the clinical cutoff point. Because it is impossible for a slice to be larger than the pie it is cut out of, neither report can have more than 25 molecular hits above the clinical cutoff. I refer to this deductive fact, and to the number 25, as the “deductive ceiling.” We use this to give the 1st report the best footing mathematically possible during its reconciliation with the 2nd report. In these equations, we are only concerned with the limit of possibility: 25. So for the sake of simplifying the matter to a clear deductive equation, I will sometimes speak of this maximum 25 as if an estimate. This allows us to work with a fixed number, instead of a cumbersome range of numbers. Later in the report we will deal with actual estimates. |
| Deductive Floor | Conversely, because the 1st report had a total number of 100 molecular hits, there could not be less than 75 such hits below the clinical cutoff. That is, if the maximum number of hits above the cutoff is 25, then that leaves 100 - 25 = 75 minimum hits below the cutoff. I refer to this as the “deductive floor.” For the sake of simplifying the matter to a clear deductive equation, I will sometimes speak of this minimum 75 as if it were an estimate. This allows us to work with a fixed number, instead of a range. Later in the report we will deal with actual estimates. |
| DLCN | Dutch Lipid Clinic Network criteria: If I use the terms “clinical,” I refer to the DLCN clinical scoring system as used by the authors of the reports in question. I might write, “above the clinical detection point” or “above the clinical cutoff point.” By this I mean a passing score, according to the authors, using the DLCN system: “Definite and Probable.” If I say “above the clinical cutoff” or “above the detection point,” I refer to the higher scores, and not necessarily to the order of rows in a given table. For example, the authors provide a table where the higher scores are actually set in the lower rows of a table. These would be nonetheless “above” the DLCN cutoff point – meaning they have sufficiently high scores to be regarded as having “FH.” They look like they might have FH. The clinical test is used in contradistinction to a molecular test: those who look like they might carry a mutation versus those who are confirmed to carry a mutation. Damgaard found that of those who scored in the top two DLCN categories, 50% were nonetheless not found to carry a mutation. |
| FH | Familial (inherited) Hypercholesterolemia. Also known as Heterozygous FH (HeFH). Strictly speaking it is determined by mutations in the LDL receptor (LDLR). Around 2,000 different LDLR mutations have been discovered. Thus, there is a “spectrum” of FH LDLR mutations. However, clinically, other diseases and environmental factors can have the same outward appearance (same “phenotype”). This permits an ambiguity which sometimes leaves FH as a kind of umbrella-term under which other diseases and environmental factors co-exist. As with most linguistic ambiguities, this confusion is a cultural reality. However, even among professionals and experts, this dual use of the term has been exploited by the industry. |
| Non-FH | Nonfamilial (non-inherited) Hypercholesterolemia |
| FDB | Familial Defective Apolipoprotein B100. This is a mutation in a different location: from the molecular perspective, FH refers to the receptor and FDB refers to the ligand (APOB). FDB is generally milder than FH and is rare outside of European ancestry. Unlike FH, there are not a wide variety of harmful FDB mutations. They are almost always R3500Q and R3500W. And in any event, within the data used by the authors there is no “spectrum” for FDB beyond R3500Q and R3500W. |
| ADH | Autosomal Dominant Hypercholesterolemia is the true umbrella term under which FH and FDB are distinctive constituents. While the ambiguity inherent in a clinical use of “FH” conceals the molecular nature of its constituents, “ADH” clarifies those constituents at the molecular level. Given that FH is an inherited disease, where the mutations are the key point, responsible treatment demands a careful distinction between the terms FH and FDB ... which the authors of the Authoritative report do not make. Rather these authors skip over expert definition and exploit the confusion by avoiding the use of “ADH” as a term in the entire Authoritative report. (There are other molecular constituents under this umbrella; however, they do not play a role in the mathematical and logical abuses that I outline in my analysis.) |
| Genotype | “All or part of the genetic constitution of an individual or group” ~ Merriam-Webster’s |
| Phenotype | “The visible properties of an organism that are produced by the interaction of the genotype and the environment.” ~ Merriam-Webster’s |
| Spectrum | As it applies to the 2nd report, the set of known, distinct mutations within FH and/or FDB. |
**Proband**

Sometimes referred to as an “index patient.” A single member of a family is isolated. For example, if related grandparents, parents, and children all have FH, only one of them will be counted as a proband. There are two key sets of mutation carriers. In my analysis, probands should be understood in the context of the mutation spectrum. For mathematical purposes, Top4 probands would be a distinct set from the Top4 mutation hits among the general population. Although problematic, the authors think of these two sets of numbers as parallel, where the distribution of probands within the spectrum is symmetrical to the distribution of mutation hits within the general population. For example, if the 55 Top4 probands make up 38.7% of the 142 probands in the entire spectrum, then we should carry that same proportion over and treat the 174 Top4 mutation hits within the Copenhagen population as 38.7% of the total prevalence. With this, the authors derive total prevalence: $174 \div 0.387 = 450$. (See illustration below.)

**Top4**

This is my usage and specific to my analysis. By this I refer to the four most frequently occurring mutations within FH and FDB combined, according to their use in the 1st and 2nd reports. This term works in two distinct contexts: it can refer to probands within the spectrum but also to mutation carriers in the general population study. For example, in the 2nd report, there were 55 probands with Top4 mutations within the spectrum and there were 174 carriers of Top4 mutations within the Copenhagen population sample. See illustration below and page 67.

**209 or 184 clinical results**

*When I refer to 209 or the adjusted 184 as clinical results, I refer to the number of clinical hits after excluding Top4 carriers.* An estimated 15 are shared between both samples, and because we include them in the 100 Top4 molecular, we will leave them out of the Clinical total, so as not to count them twice. 309 – 100 Top4 molecular = 209 results clinical results, i.e., after excluding Top4. See pages 73 and 64.

**Ex-Top4**

This is my usage and specific to my analysis. The Top4 probands are calculated by the 2nd report to be 38.7% of total probands within the mutation spectrum. The authors then carry over this proportion to the population study: they calculate the total mutation carriers by dividing the Top4 mutation carriers by .387. I use “Ex-Top4” to refer, not to the total of mutation carriers (or probands), but only to that portion which is counterpart to the Top4. (Total carriers – Top4 carriers = Ex-Top4 carriers ... or, Total Probands – Top4 probands = Ex-Top4 probands.) See illustration below and page 67. Importantly, according to the authors’ data, all Ex-Top4 are FH LDLR, and there are no FDB APOB included.

**Top3**

After removing FDB APOB from the Top4, only the three most frequent mutations remain and they are all FH LDLR.

---

**Table: Top4 Probands within Spectrum**

<table>
<thead>
<tr>
<th>Mutation spectrum, number (%)</th>
<th>Top4: all are FH LDLR</th>
<th>Top3: all are FH LDLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB, R3500G/W</td>
<td>19 (13%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>LDLR, W350X</td>
<td>21 (15%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>LDLR, W577X</td>
<td>13 (9%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>LDLR, W758X</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Probands with pathogenic mutations*</td>
<td>142 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total Top4: 174</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Top4: 63, all are FH LDLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FDB APOB: 111</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Diagram: Top4 molecular hits within Copenhagen General Population**

Supplementary Table 3. Participants in Copenhagen General Population study by carrier status of low-density lipoprotein receptor (LDLR) and apolipoprotein B (APOB) mutations.
Key Data from the Danish reports (Authoritative report has no fundamental data of its own)

### Table 1

<table>
<thead>
<tr>
<th>Inclusion period</th>
<th>2005-2014</th>
<th>At least two of three criteria fulfilled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol=6 mmol/L, if age &lt; 40 years and at least one of following criteria:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Tendon xanthomas in patient or close relative.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) First-degree relative with LDL cholesterol ≥ 8 mmol/L in an adult or ≥ 6 mmol/L in a child &lt; 10 years.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Coronary or vascular disease before age 40 years in first-degree relative or before age 55 years in second-degree relative(s).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation spectrum, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE; R350Q/W</td>
<td>19 (3%)</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>LDL, W66G</td>
<td>21 (5%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>LDL, R275X</td>
<td>11 (6%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>LDL, R580S</td>
<td>21 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>LDL variant singletons*</td>
<td>80 (54%)</td>
<td>80 (54%)</td>
</tr>
<tr>
<td>LDL deletions/insertions*</td>
<td>7 (5%)</td>
<td>Not screened for</td>
</tr>
<tr>
<td>PCSK9 mutations*</td>
<td>0 (0%)</td>
<td>Not screened for</td>
</tr>
<tr>
<td>Probands with pathogenic mutations*</td>
<td>142 (100%)</td>
<td>135 (100%)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Version</td>
<td>Corrected Version</td>
</tr>
<tr>
<td>Unlikely FH</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Possible FH</td>
<td>3 to 4</td>
</tr>
<tr>
<td>Probable FH</td>
<td>5 to 7</td>
</tr>
<tr>
<td>Definite FH</td>
<td>&gt; 7</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Diagnostic probability</th>
<th>Definite/probable, n = 502</th>
<th>Possible, n = 4,295</th>
<th>Unlikely, n = 64,219</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>First-degree relative with premature cardiovascular disease or First-degree relative with known elevated cholesterol levels</td>
<td>9</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Personal clinical history</td>
<td>Patient with premature CAD</td>
<td>50</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td>Patient with premature cerebral or peripheral vascular disease</td>
<td>Plasma cholesterol, LDL-cholesterol in mmol/L*</td>
<td>6.5–6.4 (250–329 mg/dl)</td>
<td>32</td>
<td>79</td>
</tr>
<tr>
<td>5.0–6.4 (190–249 mg/dl)</td>
<td>32</td>
<td>79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4.0–4.9 (155–189 mg/dl)</td>
<td>9</td>
<td>9</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>&lt;4.0 (&lt;155 mg/dl)</td>
<td>2</td>
<td>12</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Genetic analysis</td>
<td>LDL (W235X, W66G, W556S) or APOE (R350Q/W) mutations (%)</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are percentages of individuals within each diagnostic group fulfilling each criterion.
1st report false positive %; the source for the Authoritative report

<table>
<thead>
<tr>
<th>False Positives</th>
<th>Academic:</th>
<th>Real-World:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Maximum Top4 Mathematically possible above the clinical cutoff</td>
<td>51%</td>
<td>69%</td>
</tr>
<tr>
<td>Using Reasonable Estimate for Top4 originally above clinical cutoff</td>
<td>55%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Using deductive ceiling, Academic results, total population screened

<table>
<thead>
<tr>
<th>Minimum False Positives</th>
<th>Relevant Results</th>
<th>False Positive %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Maximum Top4 mathematically available above the clinical cutoff.</td>
<td>Top4 detected</td>
<td>Ex-Top4 derived</td>
</tr>
<tr>
<td>Minimum Top4 mathematically available below the clinical cutoff. Impractical to locate included.</td>
<td>75</td>
<td>These carriers abandoned by methodology</td>
</tr>
</tbody>
</table>

Using deductive ceiling, Accepting that screening is impractical below clinical cutoff

<table>
<thead>
<tr>
<th>Minimum False Positives</th>
<th>Relevant Results</th>
<th>False Positive %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Maximum Top4 mathematically available above the clinical cutoff.</td>
<td>Top4 detected</td>
<td>Ex-Top4 derived</td>
</tr>
<tr>
<td>Minimum Top4 mathematically available below the clinical cutoff. Impractical to locate excluded.</td>
<td>Not practical</td>
<td>Not practical</td>
</tr>
</tbody>
</table>

Reasonable estimate for Top4, Academic results, total population screened

<table>
<thead>
<tr>
<th>Minimum False Positives</th>
<th>Relevant Results</th>
<th>False Positive %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Top4 available above the clinical cutoff.</td>
<td>Top4 detected</td>
<td>Ex-Top4 derived</td>
</tr>
<tr>
<td>Consequent Top4 remaining below the clinical cutoff. Impractical to locate included.</td>
<td>83</td>
<td>These carriers abandoned by methodology</td>
</tr>
</tbody>
</table>

Reasonable estimate for Top4, Accepting that screening is impractical below clinical cutoff

<table>
<thead>
<tr>
<th>Minimum False Positives</th>
<th>Relevant Results</th>
<th>False Positive %</th>
</tr>
</thead>
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<tr>
<td>Consequent Top4 remaining below the clinical cutoff. Impractical to locate excluded.</td>
<td>Not practical</td>
<td>Not practical</td>
</tr>
</tbody>
</table>
**FH and FDB conflation: Introduction to the confusion**

Recently, reports are informing the medical community that HeFH, or “FH,” has a prevalence of 1 in 200. There is a lot of confusion involved with this result. Let’s start with the terminology. The medical community is not settled on the names of the diseases in question. On the right is the FDA indication for the drug Praluent. It clearly designates FH. I don’t see a mention of Familial Defective ApoB100 -- “FDB.”

Below is TUFTS Health Plan. It clearly includes FDB as “FH.”

![Image](https://tuftshealthplan.com/documents/providers/guidelines/pharmacy-medical-necessity-guidelines/pcsk9-comm-direct)

Culturally, there is some confusion about what FH is and what it isn’t. And one will find FDB and FH both referred to as FH. Strictly speaking, however, FH and FDB are two different inherited diseases. The 1st, Authoritative, 2nd, and Regeneron reports all blend FH and FDB due to available linguistic ambiguity and refer to the natural mathematical result as a larger FH prevalence count.

The established prevalence of FH-as-LDLR mutation is 1:500. Of FDB-as-APOB mutation, it is 1:1000. If I combine FH and FDB, I mathematically derive a prevalence of 1:333. If I call these combined patients “FH,” have I really found more people or have I joined two known populations under a single umbrella-term, “FH,” which then requires that I follow through with the required math?

In a parallel example, due to ambiguous usage, the word “animal” sometimes refers to the entire kingdom of living things, including birds and reptiles, and even protozoans. Other times it means mammals exclusively. So in one context I could speak of cows, sheep, pigs, and geese under the subject of “animals.” In another context I might use the word animal in contrast to birds, in which case it is clear that I use “animal” to refer exclusively to mammals. It would be hoped that I would be responsible and effective in my use of words which are vulnerable to such ambiguities. I have 10 mammals that I call

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112 Pharmacy Medical Necessity Guidelines: PCSK9 Inhibitor Therapy Effective: January 12, 2015. (https://tuftshealthplan.com/documents/providers/guidelines/pharmacy-medical-necessity-guidelines/pcsk9-comm-direct) Other insurance companies are clearly on board with using FH as the umbrella term and setting FDB under it.
“animals” and 10 birds that I include in a larger count of “animals.” I now have 20 animals and engage in a conversation with someone who, in the context, thinks I’m talking about mammals and so I now have 20 mammals? Could I really say that I had more mammals than previously thought? This is what is happening here. We don’t have any more animals or mammals than we had before. We simply played a shell game with definitions.

However, for the uninitiated, the reports create a very real impression that the FH addressable market is much larger than previously thought, taking advantage of the ambiguous cultural usage. The word “FH” has clinical and cultural usages that can refer to all who merely look like they might have an FH mutation in the LDL-Receptor (LDL-R). This includes those who look like FH carriers due to environmental factors but who do not actually have an LDL-R mutation. However, mutations other than the LDLR can affect cholesterol levels in similar ways. One of these is APOB100, the carriers of which are diagnosed with “FDB.” 113 The FDB mutations are almost exclusively restricted to R3500Q/W. The point here is that they are distinct from FH LDL-R mutations.

Strictly, both FH and FDB fall under the name of “Autosomal Dominant Hypercholesterolemia” or “ADH.” However, this umbrella-term does not seem to have taken hold within the academic and medical communities. The industry still needs to sort out the ambiguous usage of “FH,” which is often used as the umbrella-term itself. With the phenotypic – “looks like” -- we have a bird’s eye view of an umbrella with “FH” painted on top and we cannot see the molecular constituents under it. With “ADH,” a molecular perspective, we are at ground level and see that FH and FDB are distinct and under that umbrella.

There is a Clinical Pharmacology Review of Sanofi’s Praluent found on FDA.GOV. 114 In the Appendix it lists two clinical diagnostic systems. In “Simon Broome Register Criteria for Heterozygous Familial Hypercholesterolemia” it includes FDB’s APOB mutation. On the very next page we find the “WHO Criteria (Dutch Lipid Network clinical criteria)” which lists only the LDL-receptor mutation.

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113 There are a few points peripheral to the current topic but relevant to the entirety of this analysis.

- Only two APOB mutations are considered severe and prevalent enough to be worth screening for. One of these two is nonetheless very rare.
- The more prevalent, R3500Q, is rare outside of central European ancestry.
- They are milder than their FH (LDLR) counterparts, and therefore they are expensive and time consuming to detect. Carriers may not even require risky treatment.

114 CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125559Orig1s000 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000ClinPharmR.pdf
In this section of my analysis, I’m not asking a medical question or asking what should and should not be treated; I’m only trying to find a precise definition when moving from one document to another. Which umbrella term should or should not be used? We’ll have to wait that out. The dust has not settled. Many insurance companies are clearly accepting FDB as FH, and it appears that ADH has not dominated as the umbrella term. Where is the FDA on this? As an FDA assigned indication, does FH include FDB? Was an indication added without the paperwork?

But that is not the subject on the current analysis. What concerns us here is the linguistic conflation. Accounting for it, the prevalence for HeFH returns to the established 1:500. The claim that more people have been found is false.
Cascade Screening in the USA is not practiced

“Cascade Screening” is an effective method of locating ADH carriers: it makes use of genealogy and tracks down and tests relatives of known cases. Since FH is a genetically inherited disease the advantages here should be obvious, and as expected, the molecular hit-rate is high. However, this efficiency is not attractive to the pharmaceutical industry, even if systemically possible, because the majority of carriers have milder consequences of the mutations than previously thought, as we see in the authors’ own data. It is no surprise then that industry-funded authors prefer clinical screening. Here is the concluding sentence to the 2nd report: “One must treat the phenotype not the genotype, and LDL-cholesterol should be lowered as early as possible to recommended levels regardless of information on mutation.” Again, FH is a genetically inherited disease and to prefer the phenotypic appearance of a disease to the genotypic print of that disease is the same as having a detective prefer circumstantial evidence when a forensic chain of facts is available.

Here is a summary of Cascade Screening in the United States: “There are currently no systematic approaches to the identification of FH patients or to cascade screening of their relatives in the United States. In addition, our health care system lacks key structural elements to facilitate the collection of national longitudinal data to measure and track the clinical progress of diagnosed patients.” ~ Am Heart J. 2014 December; 168(6): 807–811. doi:10.1016/j.ahj.2014.09.001, “Reducing the burden of disease and death from familial hypercholesterolemia: A call to action” -- Joshua W. Knowles, et al.

“Ms. Sturm observed that it has been shown, based on data from other countries, that FH cascade screening – systematic family tracing – can be cost effective, and further, that cascade screening that combines genetic testing plus lipid testing is more cost-effective than a lipid panel alone. However, she said, while detection of pathogenic LDLR, APOB, or PCSK9 provides an unequivocal diagnosis of FH, such genetic testing has not been systematically incorporated in the US, and there are no US guidelines recommending genetic testing in FH. In the US, therefore, genetic testing is not the standard of care, even though it is considered the diagnostic gold standard. Ms. Sturm noted that in the US, clinical genetic testing is available via multiple commercial laboratories, but these vary in clinical sensitivity, cost, and health insurance billable allowances. Physicians who want genetic testing to confirm index cases and screen family members are often deterred by the knowledge that a genetic test for FH can be ordered but not necessarily reimbursed. In addition, cardiologists and other clinicians may be confused about when to order a genetic test.” ~ Amy Sturm MS, CGC (Clinical Associate Professor and Certified Genetic Counselor, Division of Human Genetics; Associate Professor, Internal Medicine; Ohio State University), Proceedings of the FH Foundation’s inaugural Familial Hypercholesterolemia Summit: Awareness to Action Annapolis, Maryland — September 18th & 19th, 2013
Evidence that half of the APOB count may be irrelevant

(From report to report the APOB relevant to this analysis has many synonyms. What concerns us here is that the Regeneron-associated authors’ p.Arg3558Cys is used by other authors as Arg3531Cys and R3531C. See page 131 for references to these synonyms.)


“Arg3531Cys

The Arg3531Cys mutation has previously been identified in eight subjects,6,14,15 six of whom had hypercholesterolemia. However, all eight carriers were identified among either patients with hyperlipidemia who were attending lipid clinics6,15 or patients with coronary artery disease:4; therefore, the presence of hyperlipidemia could be a consequence of the study design.”

....

The one patient in our study who had ischemic heart disease and the Arg3531Cys mutation, a 77-year-old man, was the only one of eight carriers who also had hypercholesterolemia. He did not have a family history of either hypercholesterolemia or premature ischemic heart disease. It therefore seems likely that this patient may have had another cause of hypercholesterolemia. Taken together, the absence of simple cosegregation in families, the absence of a family history in our patient with coronary artery disease, and the complete absence of hypercholesterolemia in any carriers in the general population in our study suggest that this mutation is not sufficient to cause hypercholesterolemia.

Although a previous study suggested a borderline overrepresentation of the Arg3531Cys mutation in patients with coronary artery disease as compared with healthy controls,15 our results suggest that this mutation, in keeping with the absence of an association with hypercholesterolemia, is also not associated with an increased risk of ischemic heart disease.

[In the following, only Arg3500Gln, AKA R3500Q, is FDB, and not Arg3531Cys, AKA p.Arg3558Cys.]

In conclusion, our results suggest that the Arg3500Gln mutation is at present the only known APOB mutation worth screening for in white patients with hypercholesterolemia or ischemic heart disease and their relatives.


(See page 131 for synonymous use of R3531C.)
“APOB-R3531C proband screening suffered from ascertainment bias attributable to patient status.” ....

“Discussion

There is no doubt that the R3531C mutation causes reduced binding of LDL to the LDL receptor in vitro. However, our results additionally support that this reduction is not sufficient to cause hypercholesterolemia in vivo in heterozygotes. The evidence that the R3531C mutation alone does not cause hypercholesterolemia stems from functional, epidemiological, and linkage analysis. ....

In conclusion, the APOB-R3531C substitution, in view of its in vitro effects and our family study, is possibly a susceptibility mutation that, when present with other factors (genetic or environmental), slightly increases cholesterolemia. However, it is not sufficient in itself to cause hypercholesterolemia and should not be considered as an allelic variant leading to FDB.”

“Major Apolipoprotein B-100 Mutations in Lipoprotein,” Metabolism and Atherosclerosis, M. VRABLÖK, et al.

(See page 131 for synonymous use of R3531C.)

“These are mutations leading to amino acid substitution at positions 3500 (R3500Q and R3500W) and 3531 (R3531C) that have been shown to decrease the binding affinity of apoB-100 in vitro. However, only the former mutations have been unequivocally demonstrated to cause hyperlipidemia in vivo.” ....

“The incidence of the disorder in patients is similar as in the general population which is in accordance with the notion that R3531C does not cause hypercholesterolemia.”

“Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease, Consensus Statement of the European Atherosclerosis Society”; Børge G. Nordestgaard, et al.

This is the same Nordestgaard in the TYBJÆRG-HANSEN study mentioned on page 129, where it was declared “that the Arg3500Gln mutation is at present the only known APOB mutation worth screening for in white patients ....”

Now here is Nordestgaard again in the Authoritative report, declaring that there is only one relevant APOB mutation, and it is not Arg3558Cys. (Again, synonyms are present: p.Arg3527Gln = R3500Q = Arg3500Gln. See page 132.)

“Currently, >1200 mutations have been documented worldwide in LDLR; these affect all functional domains of the LDL receptor protein and include single-nucleotide mutations, copy number variations, and splicing mutations throughout the LDLR gene. A single mutation, Arg3500Gln, is the only common FH-related mutation in APOB, while >20 different mutations have been detected in PCSK9. Heterozygous LDLR, APOB, and PCSK9 mutations are found in >90, ~5, and ~1%, respectively, of heterozygous FH subjects with a causative mutation.
Synonymous usage: p.Arg3558Cys = Arg3531Cys and R3531C.

From report to report the APOB relevant to this analysis has many synonyms. What concerns us here is that the Regeneron-associated authors’ p.Arg3558Cys is used by other authors as Arg3531Cys and R3531C.

Below, sources for synonymous usage, presented in their own text:

- **SNPedia**: rs12713559, also known as c.10672C>T, p.Arg3558Cys, R3558C and R3531C, is a SNP in the APOB apolipoprotein B gene. The risk allele is A according to 23andMe, which tests for this SNP in regard to familial hypercholesterolemia type B, and where they note that the evidence is unclear about whether this mutation is causative on its own. In SNPedia, where we use the orientation as defined by dbSNP, the risk allele is rs12713559(T). [https://www.snpedia.com/index.php/Rs12713559](https://www.snpedia.com/index.php/Rs12713559)

Below, in the very text where Arg3531Cys is used, the referenced material uses R3531C.

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**Mutations in the Apolipoprotein B Gene, Hypercholesterolemia, and the Risk of Ischemic Heart Disease**

**Association of Mutations in the Apolipoprotein B Gene with Hypercholesterolemia and the Risk of Ischemic Heart Disease**


**Arg3531Cys**

The Arg3531Cys mutation has previously been identified in eight subjects,8,14,15 six of whom had hypercholesterolemia. However, all eight carriers were

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Synonymous usage: p.Arg3527Gln = R3500Q and Arg3500Gln

Also, “The authors developed an amplification refractory mutation system (ARMS) specifically designed to detect 11 mutations in the LDLR gene, one common mutation in the APOB gene (p.Arg3527Gln, formally R3500Q) and one mutation in the PCSK9 gene (p.Asp374Tyr, D374Y).” ~ Genetic screening for homozygous and heterozygous familial hypercholesterolemia, Maria C Izar, et al

See also:
http://ltd.aruplab.com/Tests/Pub/0055654
http://cardiovascmcd.com/?page=article&article_id=29134
Unanswered Email to Corresponding Author

Breakdown of APOB and LDLR among those in the cardiac catheterization laboratory

Mon 5/15/2017 10:28 AM

Tom@gesinger.edu <tom@gesinger.edu>

Dear Dr. Michael F. Murray,

RE: Genetic identification of familial hypercholesterolemia within a single U.S. healthcare system.

The results were broken down into a combined population of 50,726 and accompanying this population was a breakdown of APOB and LDLR. (EG, 102 vs. 98)

But I could not find a breakdown of APOB and LDLR among the 6,747 from the Lab. Did I miss it? Or can you let me know what that breakdown is?

And/or what was the breakdown in the unselected 43,979?

Also, how many of the 6,747 and 43,979 were p.arg3558Cys?

Thank you.

My next trip to Las Vegas would include a wager ... a calculation based upon a reversal of the disclosed selection bias:

- There will be very few APOB in the 6,747-cohort relative to LDLR. The net result in the 43,979 will include a preponderance of APOB over LDLR and would be very conspicuous.
- There will not be more than 1 or 2, and very probably zero p.arg3558Cys among the 6,747. They are notably mild *in vivo*. And if present, that 1 or 2 would most likely be here because of *other* factors.

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\[115\] This assumes the Amish were not overrepresented in this group.
Research derived from the Netherlands: *founder effect* is irrelevant to general prevalence rates.

In SEC filed documents, Sandford D. Smith (CEO) and Gregory D. Perry (CFO) cite an Aegerion funded research paper to promote an extreme prevalence rate for the US and world. This paper references a study of the Netherlands’ population, which has already been documented to suffer from “*founder effect*” —a genetic anomaly which results in *high concentrations of a given genetic trait* within a specific population. As such, the data derived from the Netherlands is wholly irrelevant to the HoFH population in the USA. *By definition, an unusual situation cannot represent a usual situation.* Aegerion thus misrepresents its addressable market when using this report to promote its prospects.

The lead author of this 2014 EAS paper is Marina Cuchel, who was also deeply involved with Aegerion’s clinical trials. She declared that HoFH had a prevalence of 1:1,000,000 — which would be about 300 patients in the USA. (The Aegerion CEO’s prevalence claim was 1,000% higher.) Her latest paper cites a different prevalence based on the Netherlands’ population. It should be noted that Aegerion has paid her, and others, “honoraria for lectures/advisory boards, consultancy, travel support and/or research grants.”

The relevant passage from the 2014 EAS paper follows.

> reported due to founder effects. However, recent studies in unselected general populations suggest that the prevalence of HeFH based on the Dutch Lipid Clinic Network criteria may be as high as 1 in ~200 or, for molecularly defined HeFH, 1 in 244. Consequently, HoFH may affect as many as 1 in 160,000–300,000 people (*Figure 1*).

Footnote #4 in the above actually refers to a specific study of whites of Danish descent — even though it is portrayed here and in the footnotes as a study of the general population. We will deal with this obfuscation later. Our focus at this point is on the other prevalence estimate, cited in footnote #5. It is the study of FH in the Netherlands:


117 Authors on the Netherlands’ study received money from Amgen, Regeneron, Aegerion, and others. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype—phenotype relationship, and clinical outcome. Barbara Sjouke, et al.

118 “Autosomal dominant hypercholesterolemia” is another name for “familial hypercholesterolemia.”
• Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome Barbara Sjouke, D. Meeike Kusters, Joep C. Defesche ... et al.

This study of HoFH in the Netherlands is far from representative of general prevalence. As it turns out two of the very scientists just cited above also did previous work demonstrating the existence of founder effect in the Netherlands. Here is a brief explanation of founder effect from a comprehensive study, “A HuGE Prevalence Review”:

As shown in table 4, the frequency of heterozygous FH is considerably higher than 1/500 in some populations, and the elevated frequency is generally attributed to a founder effect. A founder effect occurs when a subpopulation is formed through the immigration of a small number of “founder” subjects, followed by a population expansion. If, by chance, some of the founders had FH, then genetic drift could lead to a high proportion of affected subjects who share specific mutations introduced by the founders. Such founder effects are thought to influence the spectrum of FH mutations in French Canadians; South African Afrikaners, Jews, and Indians; Tunisians; Christian Lebanese; Icelanders; and Finns (for review, see the article by Goldstein et al.). These founder populations have a frequency of FH ranging from 1/411 for North Karelians of Finland to 1/67 (1.5 percent) for Ashkenazi Jews in South Africa.¹¹⁹

It is easy to see that data derived from a population influenced by founder effect cannot reasonably be used as a proxy for the “general population.” For example, it is not reasonable to take the extreme prevalence of 1 in 67 among the Ashkenazi Jews of South Africa and argue that estimates for USA or world prevalence must therefore be adjusted. But this is exactly what is done with the 2014 EAS report, using the Netherlands for comparison.

Both Joep C. Defesche’s and D. Meeike Kusters’ names appear on the source¹²⁰ for the 2014 EAS report. Yet both had previously published work on the existence of founder effect in the Netherlands. Here is their previous work, titled “Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes.”

Conclusions: Phenotypes with regard to LDL-C levels varied between the 12 most prevalent FH mutations. For most of these mutations a founder effect was observed. Our observations can have implications with regard to the efficiency of molecular screening and physician’s perception of FH, and understanding the prevalence and distribution of homozygous patients in the Netherlands.¹²¹


The above section -- “Conclusions” -- was from the abstract on page 124 of the publication. What follows is from “Discussion” and “Conclusion” at the end of the paper, on pages 132 and 135 respectively.

Discussion

For this study, we determined the geographical distribution of the 12 most common mutations, which represent 64% of all Dutch FH patients. We demonstrated that almost all common mutations showed a clearly marked region of preference, suggesting the existence of a founder effect. This can be explained by the occurrence of a local founder mutation in combination with limited migration, possibly attributable to the geographical isolation in the past, as in West Friesland and the islands of Noord and Zuid Beveland, the two regions with the highest prevalence of mutations per se. The phenomenon of geographical preference of FH causing mutations can have several clinical implications.

Conclusion: Although more than 550 different FH mutations are identified in the Netherlands, for most of the 12 most prevalent Dutch mutations a founder effect can be observed, resulting in differences in geographical prevalence across the Netherlands. This can be explained by local founder effects plus limited migration, which is also reflected by the fact that neighbouring countries and countries were the Dutch used to go, share the same mutations. The high prevalence and typical distribution of Dutch homozygous patients can also be understood by these founder effects. Molecular screening can be more efficient if it is tailored to the allele frequency distribution of the Dutch population.

It is clear that a population documented to be influenced by founder effect cannot be used as a proxy for the general population. By promoting this study as relevant, when in fact responsible players must know that it is irrelevant, Aegerion has misrepresented its addressable market. The source material of this study was re-published by way of Aegerion’s funding the 2014 EAS report and it is promoted by Aegerion in SEC filed documents, which are signed by CEO Sandford Smith.
Denmark’s “intermediate” FH-FDB prevalence is somewhere between regions with full founder effect and melting pots such as Germany and the USA.

The fact that the FH population is unusual makes it by definition inapplicable a general population which is not dominated by Founder Effect.

*FH is genetically heterogeneous, and in Denmark the mutational spectrum is intermediate, with APOB and LDLR mutations accounting for the majority of mutations, and in particular three mutations in the LDLR gene accounting for 36% of known LDLR mutations in FH patients (12, 13). ~ Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication: Marianne Benn, Gerald F. Watts, Anne Tybjaerg-Hansen, and Børge G. Nordestgaard J Clin Endocrin Metab. First published ahead of print August 14, 2012 as doi:10.1210/jc.2012-1563


Here, Jensen, et al, reported that the Danes were somewhere between outright founder effect and those considered fully heterogeneous.

*The Danish spectrum of 29 different mutations, five of which account for almost half of heterozygous FH, is intermediate between that of countries such as South Africa, where three mutations cause 95% of heterozygous FH in the Afrikaners, and Germany or England, where there are many more mutations. ~ Spectrum of LDL receptor gene mutations in Denmark: Implications for molecular diagnostic strategy in heterozygous familial hypercholesterolemia, November 1999, DOI: 10.1016/S0021-9150(99)00158-6 · Source: PubMed, H.K. Jensen, et al.

The above is expanded upon later in the paper. Denmark is somewhere in the middle of outright Founder Effect and a heterogeneous population.

*Across nations, the spectrum of LDL receptor gene mutations is rather complex (Fig. 2). In populations such as Christian Lebanese [26], Ashkenazi and Sephardic Jews [27,28], Druze Arabs [29], South African Afrikaners [11], French-Canadians [30], Icelanders [31], and Finns [32], a few mutations predominate due to founder effects. In countries as Japan [33], Germany [34] or England [10,12], many more mutations produce a highly heterogeneous picture. The Danish spectrum of 29 different mutations, five of which account for almost half of heterozygous FH, the spectra seen in Norway [35] and Greece [36] are intermediate between the above mentioned populations. ~ Spectrum of LDL receptor gene mutations in Denmark: Implications for molecular diagnostic strategy in heterozygous familial hypercholesterolemia, November 1999, DOI: 10.1016/S0021-9150(99)00158-6 Source: PubMed, H.K. Jensen, et al.

The population study in Denmark in the Northern/central European region where the APOB defect originated. It is well documented that this area has a higher prevalence than external areas.

*Thus, most countries appear to have cohorts within the general population with increased prevalence of FH due to relatively few mutations that no doubt reflect a
history of cultural and/or geographic isolation. The latter include Denmark with five mutations occurring in 50% of FH patients and Tunisia with a FH prevalence of about 1 in 165. ~ “Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution,” Khemanganee, et al.

FDB APOB has unusually high prevalence in Northern and Central Europe

Although attempts at deducing the genetic history of FDB are limited by uncertainties in reconstructing population movements in the prehistoric past, it has been suggested that it originated in a person thought to be a Celtic (Helvetii) ancestor whose home was originally situated between the rivers Rhine and Maine and whose descendants migrated into the northwest of modern Switzerland more than 2,000 years before the present. It is also suggested that the low prevalence of FDB in Mediterranean peoples and its absence in Turkey is due to the migration barriers created by the Alps and the Pyrenees, hence its relative confinement to the region northwards of central Europe. Although rarely occurring in Italy, Sicily and the general Spanish population, FDB Arg3527Gln is a common cause of ADH in Galicia, a region in northwestern Spain that was settled by Celtic people in the eleventh century BC. It accounts for a significant proportion of those with a clinical diagnosis of FH or autosomal hypercholesterolemia in other nations including Switzerland, Bulgaria, Hungary and Denmark, and is as high as 11% in the Czech Republic and Poland. ~ “Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution,” Khemanganee, et al.

Citations 118 and 119 in the above passage are presented below:


Lars Anderson wrote a very accessible article on APOB prevalence in Europe and Lancaster, PA

This Regeneron funded study cherry-picked precisely a region dominated by whites of European descent, and in a region famously influenced by founder effect. In fact a segment of this population group “probably has the highest incidence [of the R3500Q APOB mutation] worldwide.” The emphasis is mine.

*Investigators* have detected the R3500Q mutations in over thirty countries worldwide, with a high concentration of carriers in central and northern Europe. Switzerland, Germany, the Czech Republic, and Slovenia are thus areas with a high prevalence of R3500Q,22-25 but the area that probably has the highest incidence worldwide is not in Europe, but in our own Lancaster County, Pennsylvania. In 2010, population screening of members of the Old Order Amish community revealed that approximately 12% of the general Amish population carries R3500Q. This rate is consistent with a genetic “founder effect,” whereby a population bottleneck reduces genetic diversity and increases the frequency of otherwise rare alleles. As the authors of the 2010 study observe, the mutation was likely carried to Lancaster County by one of three hundred German-speaking Swiss members of the Old Order Amish Church. The gene flow rate of R3500Q into the wider Lancaster County community and its incidence among Lancasterians of Mennonite or Germanic heritage is at the moment undetermined. Still, other recessive genetic disorders associated with the Amish have previously been found in non-Amish Lancastrians, and all newborns in the state are screened for diseases associated with the Amish such as glutaric aciduria and maple syrup urine disease. As an analogous yet dominantly inherited disorder, the effect of FDB due to R3500Q on countywide health has considerable significance for the ongoing Lancaster General Health Familial Hypercholesterolemia Initiative. ~ *Familial Defective Apolipoprotein B-100 in Lancaster County and Beyond* Lars Andersen, B.A. Research assistant and site coordinator for CASCADE FH Registry The Heart & Vascular Institute.