Citation Kiting, Obscurantism and Trafficking Humans in FH Literature

(Familial Hypercholesterolemia)

“The study shows us that FH is about twice as common as it was once thought to be ...”
[‘Geisinger and Regeneron study finds life-threatening genetic disorder is substantially underdiagnosed,’ Dec. 22, 2016]

Part 1: Linguistic Manipulation through Citation Kiting in Peer Reviewed FH Literature

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Some of the companies on Wall Street who are interested in the FH population (past or present)
- NVLN  Novelion Therapeutics Inc. (Aegerion Pharmaceuticals)
- MDGL  Madrigal Pharmaceuticals Inc.
- GEMP  Gemphire Therapeutics Inc.
- ESPR  Esperion Therapeutics Inc.
- AMGN  Amgen Inc.
- REGN  Regeneron Pharmaceuticals
- MRK  Merck & Co. (Had hopes for Anacetrapib 2011 ~ 2017)
- Companies which market statins also have an interest.
Violence and Organ Manipulation: the future of human trafficking

**UN Palermo Protocol, Human Trafficking:**

1. Real people are recruited ... on a mass scale,
2. By means of deceit, deception and fraud,
3. For the commercial exploitation of their bodies as hosts for *drugs* and the commercial manipulation of their organs.

If the movie “Matrix” were brought to reality within the USA, would the scheme be prosecutable? How?

- **“Matrix”:** Human bodies are reduced to serve as mere hosts for another’s interests, with their minds deceived into thinking otherwise. All of these hosts are exploited for their corporal resource, their electrical current.
- **FH Industry:** Human bodies are reduced to serve as mere hosts for another’s commercial interests, with their minds deceived into thinking otherwise. All of these hosts are exploited for their corporal resource, their financial currency.

The [US State Department has a checklist for Human Trafficking](https://www.state.gov/j/tip/rls/tiprpt/2008/105487.htm). Two of the three criteria on this webpage are easily satisfied: recruitment and deceit. As for the third element, the State Department does not explicitly list “organ manipulation” on this page but it does mention “involuntary servitude” and “violence.”

When one is deceived into submitting one’s body for another’s profit, why wouldn’t this be a form of “involuntary servitude”? As for “violence,” ...

A) If a stranger on the street deceived me into thinking I was in urgent need of help, plied me with whiskey till I passed out, took my arm over his knee and applied immense pressure, injuring my arm, that would undoubtedly be “violence.” He could say, “but you agreed and anyway, you didn’t feel anything, did you?” ... I would counter that he deceived me first and that I would not have agreed otherwise. And my lack of feeling at the point of violence does not take away my present injury.

B) As it happened to myself as a teenager, a *doctor* performed roughly these same mechanical steps in order to set my broken arm, albeit with local anesthesia and not whiskey. That was undoubtedly “medical treatment.”

The difference between “violence” and “medical treatment” in the above is not just the presence of anesthesia, but the purpose and good faith of the doctor, and my parents’ informed consent.

C) If the doctor had lied to my parents, for commercial gain, that is, if in fact my arm had not been broken, *then the extreme force applied, injuring my arm, anesthesia or not,* would be indistinguishable from the stranger in example A above, who with equal force, and with deception, put my arm over his knee and injured me. The fact that he was officially a doctor should make no difference; otherwise there would be a license available for intentional, non-medical injury.

D) If Big Pharma cherry-picks researchers, already known to have manipulated data, and through a publication strategy deceives the downstream medical community into swapping out the real patients with the indicated disease for *others who do not have this disease,* then the *recruited* bodies of these non-indicated patients, through *deceit, involuntarily serve* the masters of the commercial scheme, with risk and injury to their bodies and their organs, and thus as victims of *violence.*
The bigger picture: Trafficking Humans

Whether by voice or by academic publication, the net result of the two crimes below is the same: **real people are swapped**. What law is broken here? The mechanics are the same as the crime I demonstrate in my analysis.

- Here is the exact same crime. Only the “vehicles” are different. Unlike the case above, no video can be decisive here; nonetheless, as my analysis demonstrates, **switching FH identification procedures swaps patients**.
If this were about science, I wouldn’t be here. What follows is not a scientific issue. If I said that two pills plus two pills do not equal five pills, I am not talking about pharmacology or medicine. Likewise, this analysis is not really about science or disease. It’s about deceptive linguistics and math. If we were in Las Vegas, it would be a magic show.

Important Note: There are two forms of FH, the heterozygous and the homozygous. The heterozygous inherited the problem from only one parent, and the homozygous from both parents. The heterozygous FH (HeFH) have a prevalence of 1 in 500. The homozygous (HoFH) have a prevalence of 1 in 1,000,000. Because this is a genetic disease there is a mathematical relationship between these two prevalence numbers. So when HeFH prevalence doubles, it also increases the estimate for HoFH prevalence1 -- and of course it goes the other way around too.

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1 How do authors in the FH industry calculate from the HeFH to the HoFH? Although calculation of HoFH from the HeFH, begins with “2pq” of the Hardy-Weinberg equation and one does not know the exact value of “q,” because “p” (or the prevalence of HoFH) is so extreme, the value of “q” will always be so close to 1 that, practically speaking, it is inconsequential when resolving “2pq.”
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<th>Title</th>
<th>Authors</th>
<th>DOI</th>
<th>Notes</th>
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<td>Earlier Report</td>
<td>2005</td>
<td>Phenotype of Heterozygotes for Low-Density Lipoprotein Receptor Mutations Identified in Different Background Populations</td>
<td>Anne Tybjærg-Hansen, Henrik kjærulf Jensen, Marianne Benn, Rolf Steffensen, Gorm Jensen, Børge G. Nordestgaard</td>
<td>10.1161/01.ATV.000149380.94984.f0</td>
<td></td>
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<tr>
<td>2011 Report</td>
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<td></td>
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<td>2013 EAS Report</td>
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<td>2014 EAS Report</td>
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<td>Doctor’s Dilemma</td>
<td>“Dr. Baum’s Language Strategy”</td>
<td>2014</td>
<td>The doctor’s dilemma in the diagnosis and care of homozygous familial hypercholesterolemia: Seth J. Baum, MD</td>
<td><a href="https://doi.org/10.1016/j.jacl.2014.09.005">https://doi.org/10.1016/j.jacl.2014.09.005</a></td>
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<td>2nd Danish Report</td>
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<td>Regeneron report</td>
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</table>
Which Wall Street companies are interested in FH Prevalence?

Big players like Amgen, Regeneron, Sanofi, Merck, and others are financially interested in FH prevalence. However, Novelion (NVLN), Gemphire (GEMP), Madrigal (MDGL) and Esperion (ESPR) are also valued according to how large or small the FH population might be. These four companies go the extra mile and actually claim prevalence estimates in their annual reports filed with the SEC. Below are screenshots I took last year of the 2017 10-Ks. The same claims are made in the 2018 10-Ks. All four claims depend upon “consensus” reports, which actually conducted no prevalence studies of their own. After chasing the literary references down to their sources, the stones upon which these prevalence claims are built are not scientific. They are linguistic and depend upon preserving asymmetry between what the authors and their readers know. The 2014 EAS HoFH prevalence estimates – 1 in 300,000 and 1 in 160,000 – are derived from citation kiting. This results in the equivocation of the (1) genetic definition of the disease and (2) diagnosed FH. Of these two, we will first look into the former, the linguistic equivocation of the genetic definition of FH. In a separate presentation, I will provide evidence of the equivocation of “FH” through the removal of key elements/steps in the diagnostic procedure.
For prevalence of homozygous FH, the difference between the Danish result of 1/160,000 and the Dutch result of 1/300,000 is large, but we must also remember that the original estimate by the Nobel Prize winner was 1/1,000,000. Even if we just consider Novelion, and not the entire industry, we can see what is at stake. What will shares of Novelion be worth with this or that prevalence figure? When raising money from investors, what value will investors place on such a company after the Dutch report? The annual price of Aegerion/Novelion’s drug, Juxtapid, has ranged from $290,000 to well over $300,000 during the last 5 years. To create a rough sketch, I used $300,000 to represent the price over these years and 320 million for the U.S. population. Then I calculated the annual addressable market per prevalence estimate according to the Danish and Dutch reports. I set these two estimates between Aegerion/Novelion’s actual Juxtapid U.S. sales during the last 5 years and an addressable market in accordance with the Nobel Prize winners’ estimate.
The two pillars to the tripled and sextupled HoFH prevalence are the Danish and Dutch reports. It is clear that these new “scientific” numbers are used for and by investors, enabling fund raising. Here are just two examples. Top right: in a 10-K for investors, prevalence is in a text devoted to Madrigal’s “market opportunity.” Below: Novelion uses these numbers, not in a scientific context, but in an investor presentation.
1-chart Summary of the Language procedure
(Skip to page 12 to begin a more detailed report. I’ll present examples, screenshots, and references.)

We can use the 2016 Regeneron report to compare the linguistic usage of FH with the already established epidemiology (left and right columns). Then we can compare the Regeneron report with the 2018 Merck Manual update (top rows versus the very last row). The Nobel Prize winners (Goldstein and Brown) have previously counted only the LDLR gene as “FH,” and they are now Regeneron directors. Now Regeneron’s 2016 study doubles prevalence by taking advantage of a series of linguistic maneuvers that took place over the last 8 years (the subject of my analysis). This was done by counting the APOB and PCSK9 mutation carriers as FH. It is doubtful that these Regeneron Directors/Nobel Prize winners, whose careers were built on the discovery of the cause of FH, the LDL receptor, did not know about the 2016 Regeneron report. Lastly, the 2018 Merck Manual update is mathematically impossible (last row).

These are Truisms:
- A whole pie is larger than one of its slices.
- Nobel Prize winners are Regeneron directors, and Regeneron’s 2016 “FH” when defined as LDLR + APOB + PCSK9 + R3531C is greater than Nobel Prize winners’ “FH” when defined as LDLR alone.

<table>
<thead>
<tr>
<th>Regeneron’s Linguistics</th>
<th>Established Epidemiology (with Regeneron’s inclusion of p.Arg3558Cys)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blending the underlying objects under one name.</td>
<td>Tracking the underlying objects of the original names.</td>
</tr>
<tr>
<td>Past</td>
<td>Present</td>
</tr>
<tr>
<td>Call LDLR mutation carriers, “FH”</td>
<td>Drop usage of “ADH” and call LDLR, APOB, PCSK9, and p.Arg3558Cys, “FH”</td>
</tr>
<tr>
<td>Call the APOB, “FDB”</td>
<td>Past “ADH” + p.Arg3558Cys = Present “FH”</td>
</tr>
<tr>
<td>Call the PCSK9, “FH3”</td>
<td>“FH” = 1:200~1:250</td>
</tr>
<tr>
<td>Call the entire group, “ADH”</td>
<td></td>
</tr>
<tr>
<td>Call p.Arg3558Cys “harmless APOB”</td>
<td></td>
</tr>
<tr>
<td>Past “ADH” ≠ past “FH”.</td>
<td></td>
</tr>
<tr>
<td>“FH” = 1:500</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rational Conclusion</th>
<th>The change is only due to linguistics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change or discovery.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The 2018 update in Merck Manual</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“FH” returns to its original usage and is defined again solely by presence of LDLR. The APOB and PCSK9 are listed separately ... again.</td>
<td>But the APOB and PCSK9 are still included in the math for the LDLR. FH as solely LDLR is said to be 1/200. This is only possible if the APOB and PCSK9 are double counted.</td>
</tr>
</tbody>
</table>
In the beginning there were three different diseases

An outline of the industry-wide “Language Strategy” to re-define the disease, Familial Hypercholesterolemia (“FH”):

To understand recent FH prevalence claims, it is more important to trace the linguistic history than to labor over the science as presented today. Once the scientific record is off course, more power applied to an erroneous assumption only sends us further astray. It’s time to stop and reevaluate where and how this vehicle of science slipped off the road.

"FH" stands for "Familial Hypercholesterolemia." It is a genetically inherited disease. Mutations in the LDL receptor (LDLR) account for a disruption of the normal processing of cholesterol, resulting in higher than average levels in the body. This was first pointed out by Nobel Prize winners Joseph Goldstein and Michael Brown. Think of the LDLR as "trucks" that connect with trailers and haul loads away. If the truck has a factory defect and breaks down, the loads sit in their trailers and pile up at the depot. In the same way, if the LDLR is consequent of a mutant gene, then cholesterol can build up in the body. In 1973, Goldstein and others estimated the prevalence of LDLR mutation carriers to be between 1/500 and 1/1,000 (screenshot on the right).

Since then other mutations have been found. For example, one mutation involves the gene encoding the ligand Apolipoprotein B-100 (APOB). Its discovery has created the need for an additional disease name, "Familial Defective apob-100" or also called, “familial ligand-defective apolipoprotein B-100" -- slight variations of the name are used, but usage of the acronym is fairly stable, "FDB." Think of this mutation as the "hitch" between the truck and the trailer, and which allows the truck to connect with and pull the load. It is a different problem from the LDLR mutation and was discovered after the calculation of FH-as-LDLR prevalence. FDB prevalence is estimated to be somewhere around 1:1,000.

Problems with PCSK9 have also been found, and this disease went by the name, “FH3.” Think of this problem in terms of magnetic scrap that the truck must drive through. If too much scrap attaches to the truck, it will weigh it down and prevent it from completing its rounds. Prevalence for FH3 is estimated to be 1:2,500.

**Note:** Amgen, Regeneron, Sanofi, and Merck have (or had) direct financial interests in the HeFH market. As for Aegerion (Novelion), Madrigal, Gemphire, and Esperion, there is a mathematical relationship between the two forms of **unequivocal** FH: HeFH and HoFH. Thus, when papers conflate the **names** of diseases to “double” the quantities of patients with HeFH, the papers also “increase” the estimated prevalence and addressable market of the rarer, HoFH.
Even as late as 2009 Goldstein and Brown continued to define FH by the presence of the LDLR mutation and estimated its prevalence to be 1:500. Below right is a photo of the Nobel Prize winners in 1985. Below left is a 2009 paper recounting their history, where prevalence was still calculated to be around 1:500.

DOI: 10.1161/ATVBAHA.108.179564.

The important point here is that at one time, there was FH—as-LDLR. Later, FDB—as-APOB arrived. Then FH3—as-PCSK9. These are three separate disease names, with three separate populations (and as we will see later, they have different degrees of severity). Changing the labels that are put on these real people -- the carriers -- does not change their number as a whole. But we need labels of course in order to communicate. So what should we call the entire group of those who inherit one of the three types of mutations? The term "Autosomal Dominant Hypercholesterolemia" (ADH) emerged. ADH was an umbrella-term under which the three types of diseases would stroll, as it were. And so, given the separate prevalence rates of the separate diseases, what would be the prevalence of all three combined, that is, what is the prevalence of "ADH?"
Passive mathematical result when aggregating known diseases together


One way to calculate prevalence is to convert each fraction to the same denominator and then add the numerators.
• \( \frac{1}{500} = \frac{5}{2500} \)
• \( \frac{1}{1000} = \frac{5}{5000} \)
• \( \frac{1}{2500} = \frac{2}{5000} \)
Total: \( 10 + 5 + 2 = \frac{17}{5000} = 1:294 \)

Table 1. Major monogenic diseases that cause severe hypercholesterolemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defective gene</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia (FH)</td>
<td>LDL-R</td>
<td>1 in 500,000</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td>LDL-R</td>
<td>1 in 500,000</td>
</tr>
<tr>
<td>Homozygous FH</td>
<td>LDL-R</td>
<td>1 in 500,000</td>
</tr>
<tr>
<td>Heterozygous FDB</td>
<td>APOB</td>
<td>1 in 1,000,000</td>
</tr>
<tr>
<td>Homozygous FDB</td>
<td>APOB</td>
<td>1 in 1,000,000</td>
</tr>
<tr>
<td>Heterozygous FH3</td>
<td>PCSK9</td>
<td>1 in 2,500,000</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>ATP7A1</td>
<td>&lt;1 in 5</td>
</tr>
<tr>
<td>Recessive autosomal</td>
<td>ATP7A1</td>
<td>&lt;1 in 5</td>
</tr>
<tr>
<td>Hypercholesterolemia (ADH)</td>
<td>ABCG5 or ABCG8</td>
<td>&lt;1 in 5</td>
</tr>
<tr>
<td>Statoroemia</td>
<td>ABCG5 or ABCG8</td>
<td>&lt;1 in 5</td>
</tr>
</tbody>
</table>

If we combine the three separate diseases and call the result, "ADH," then we simply complete the necessary math and find a prevalence of 1:294, which we can round to 1:300. This is not an exercise limited to a specialist of epidemiology. An elementary school student can do it. No study in the field is necessary -- just as no trip to the supermarket is required when tallying up items on a shopping receipt.

That was 2003. However, in 2005 Aegerion Pharmaceuticals will submit a filing with the SEC for a sale of securities.² Aegerion will focus on patients with the very rare form of familial hypercholesterolemia, those who inherited the gene defect from both parents ("homozygotes").³ In 2006, Dr. Rader receives 265,941 shares of Aegerion stock, for under $400.⁴ In 2007 he is listed as a member on Aegerion Pharmaceutical’s “Scientific Advisory Board.” (Later, from August 2013 to December 31, 2016, Dr. Rader will receive $228,000 from pharmaceutical companies – including Aegerion, Regeneron, and Sanofi, among others.⁵ Collection of this data⁶ starts in 2013, so we don’t know what payments he may have received earlier.)

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² https://www.sec.gov/Archives/edgar/vprr/0506/05065520.pdf
³ https://www.sec.gov/Archives/edgar/data/1338042/000119312507059921/ds1.htm
⁴ https://www.sec.gov/Archives/edgar/data/1338042/000119312507250821/ds1.htm
⁵ https://projects.propublica.org/docdollars/query?utf8=%E2%9C%93&query=daniel+j+rader&state=&commit=Search
⁶ Gathered through the “Physician Payments Sunshine Act,” For the particular database I accessed, see https://www.propublica.org/article/about-the-dollars-for-docs-data.
In 2011, Dr. Daniel Rade will join Dr. Anne Goldberg and others in a coordinated series of FH reports published in the Journal of Clinical Lipidology. The reports received funding from Aegerion and other pharmaceutical companies. The lead report is explicit. It admits that “in the past” FH solely referred to the LDLR mutation but tells the reader that it is going to combine the APOB and PCSK9 under the same name, “FH.” The “broader definition” effectively erases the names “FDB” and “FH3” from the scientific record.

While in 1973, Nobel Prize winner Joseph Goldstein put the prevalence of FH between 1:500 and 1:1,000, in this 2011-series of reports the prevalence range will be 1:300 to 1:500. There is no cited, external, contemporary source for 1:300. Even in other reports in this 2011 series, some citations appear to be sources for the new number, but all eventually end with the Nobel Prize winners’ 1:500.

A prevalence of 1:300 in this 2011 report is simply the passive math necessary when combining known sets into a single newly created set. Where the label “FH” was once a set beside other sets – FDB and FH3 – now the new label “FH” has consumed the other sets. By inserting the underlying mutations, APOB and PCSK9, into the FH set, the names, “FDB” and “FH3” remain unmentioned in this context. As I will show, this is an initial move toward the eventual extinction of these other names.

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9 I refer to the use of empty citations as “citation kiting.” This manipulation occurs in other, widely cited FH publications. Although the act of kiting is conspicuously simple, the consequences require elaborate presentations. In a brief presentation, some of these “fact-ectomies” will appear to be mere typos. But that is not the case: the equivocation engineered by fact-ectomy alters patient identification instructions. In prevalence this inflates the value of Wall Street traded stocks; in medicine it swaps out the genuine patients, and swaps in patients suffering from other diseases.
Because the Sunshine act is not yet effective in 2011, we don’t know what payments may have looked like before August 2013, but the authors’ conflicts of interests were inordinately large in 2011. Thirteen out of fifteen of the authors had financial ties to Merck, for example.
Here are the 2011 authors, with my commentary. In the illustration, I’ve called out payments received by most of the authors post-2013, more than $3.3 million. These payments include but are not necessarily restricted to FH related activities. Albeit in the future, a majority of the authors will be willing to accept significant payments from pharmaceutical companies.

The prestige of being a published author is an incentive. One is also declared an “expert” among one’s peers. But there is also money. We don’t know specifically what they may or may not have received in 2011. But if we add in the disclosure of pharma funding found in the 2011 reports, it is not unwarranted to speculate that financial incentives might have influenced this publication. Dr. Rader is also present. He was an Aegerion shareholder. Here he is in the years leading up to the redefinition of FH.

10 https://projects.propublica.org/docdollars/

11 See previous page.
Another person of interest is Dr. Seth Baum. \textbf{(Item 1 in the illustration below)} His online curriculum vitae tells us that he was a peer reviewer for this same Journal of Clinical Lipidology in 2011. He specializes in FH issues, and the 2011 “supplemental series” published by the journal focused on FH issues. Aegerion provided funding for this 2011 publication. We don’t know if or how much Dr. Baum received from Aegerion during 2011. We do know however that he was a speaker, consultant, and scientific advisor for Aegerion. \textbf{(2)} We also know that out of 7,000 doctors who received payment from Aegerion from late 2013 to the end of 2016, Dr. Baum was the highest paid. \textbf{(3)} Although circumstantial, these spokes radiate from the same hub: we also know that Marc Beer was Aegerion’s CEO during the relevant time period. CEO Beer is associated with the SEC, DOJ, FBI, and FDA investigations. \textbf{(4)} Although we don’t know if Dr. Goldberg and Dr. Baum knew each other, or worked together, during 2011, we do know that in 2015 they appeared together in a photo, which serves as promotional material for the FH Foundation, a charity on which Dr. Baum serves as Secretary Treasurer. Of course, the FH Foundation receives money from pharmaceutical companies. Aegerion was listed as a donor in the past. However, they are no longer listed on the FH Foundation website. Presumably, they ceased donations after the federal investigation began. (Part of the investigation included/includes Aegerion’s association with a charitable organization.)
Now let’s uncover a few more facts. In 2013 Dr. Baum was clearly promoting peer reviewed claims of FH prevalence to investors, and Wall Street analysts were clearly drawing conclusions from the scientific claims. Then in 2014, after the 2013 and 2014 EAS papers had conflated separate diseases through citation kiting, Dr. Baum explains the need for a “language strategy.” Let’s set up the time line and drop these two facts in.


- **Evolution of a definition**
  
  “HoFH is an infrequent inherited disorder usually caused by mutations in both LDL receptor alleles, which results in very high elevated plasma LDL cholesterol concentrations and very early morbidity and mortality due to accelerated atherosclerotic cardiovascular disease (ASCVD), usually before the patient turns 30 years old. In patients with HoFH, the main cause of mortality and morbidity is the aortic stenosis rather than involvement of the coronary arteries.” This was an original definition for HoFH written by the “fathers” of the disorder. This, as well as the original molecular definition, has itself mutated over the years. FH now includes autosomal dominant mutations in at least two other genes, PCSK9 and apoB 100. To further confuse the issue, molecularly defined HoFH now includes both double heterozygotes and compound heterozygotes and may also rarely involve more than two mutations. ....

- For this reason, the newer and less genetically precise terms have appropriately become embedded in our definition of HoFH. This expanded HoFH definition enables doctors to broaden their detection and care of such patients, an extraordinarily high-risk population in need of early and aggressive treatment. ..... 

- Over the past few years, it has become apparent that the current definition of HoFH (expanded from its original Goldstein and Brown view) is likely inadequate. We now have evidence that the prevalence of HoFH may be one in 160,000, whereas HeFH occurs somewhere between 1 in 200 and 1 in 300. ....

- **Reduction is order**: teaching medical practitioners to have FH as a fixture on their differential diagnostic list of LDL disorders is crucial. ....

- **The doctor’s dilemma resolved with a common language strategy**: a pragmatic approach to managing clinically severe FH” ....

- **We proffer the following clinically grounded** approach that may simplify and enhance the care of adult patients with clinically severe FH, regardless of its genetic bases.
Transparent **citation kiting** in the 2013 EAS “consensus statement”
The 2013 “consensus statement of the European Atherosclerosis Society” was published in the European Heart Journal. It can be seen below, on the right. It is the most influential statement of FH prevalence in the industry, found in FDA documents, investor presentations, patient brochures, and even in SEC 10-K filings.

It puts FH prevalence at 1/200. This number is converted in the 2014 EAS statement through the “Hardy-Weinberg” equation to the HoFH population of 1/160,000. (See 3footcrowbar.com for more detail.) I found many shenanigans in these reports, and I hope to go public with those in separate presentations. For the present purposes, we’ll focus on the **linguistic** manipulation executed by way of citation kiting. On the left is Dr. Rader’s 2003 report, with the established definition of FH: it is distinct from the APOB and PCSK9 carriers. On the right is the 2013 EAS report which cites Dr. Rader’s paper, but it conflates the diseases together. **Combining** FH, FDB, and FH3 in the 2003 report on the left leaves us with 1 in 300. Most of the 1 in 200 in the 2013 report on the right is due to this linguistic maneuver. (As for getting from 1 in 300 to 1 in 200, I will cover that in a separate presentation.)
Transparent Citation Kiting in the 2014 EAS “consensus”: how to carry a conclusion without having to reach it.

Pharma-funded publications are using readers’ suspended attention between publications to leave out facts, definitions, and even key numbers. I’ve referred to this removal during the researchers’ transfer of information as a “fact-ectomy.” As for “citation kiting,” like check kiting, it claims a value on paper which persists as a value only as long as that claim remains unreconciled with its source. The scheme is easy to see, once we’re looking for it. We just trace the “citation” back to its source, match up quantities claimed in each, account for “innovative” definitions, and then set up their respective values and terms side by side. With citation kiting, what we see is something like a relay team that cheats by switching batons, instead of passing on the original. In SEC 10-K filings this 2014 EAS report is the source for the HoFH prevalence of 1/300,000. (It also takes the 2013 EAS HeFH number and through derivation cites 1/160,000 for HoFH.) It’s not epidemiology. It’s a gimmick.

2014 Dutch Report

*Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome*

Barbara Oostwaard, D. Meulens Kusters, Iris Kindt, Joost Besseling, Joop C. Defesche

Based on 16,722,387 inhabitants, the prevalence of HoFH in the Dutch population ranged from 1 in 371,608 (95% CI: 1:287,356–1:526,316) to 1 in 407,863 (95% CI: 1:312,500–1:588,235) persons, after excluding patients from consanguineous parents. Assuming the Hardy–Weinberg equilibrium in the Dutch population, in which $p^2 = 1/407,863$, $p = 1/639$, and $q = 1 - p$, the prevalence of heterozygous FH (HeFH) (2 $p^2$) is 1 in 319 persons. The prevalence of hoFDB is 1 in 4,180,597 (95% CI: 1:210,705–1:209,021), which translates to a prevalence of heterozygous FDB of 1 in 1,023 persons.

Based on the calculated prevalences, the number of heterozygous ADH patients in the Netherlands is 68,636 (16,722,387 inhabitants *HEFH prevalence + 16,722,387 *HoFH prevalence; translating into a heterozygous ADH prevalence of 1 in 244 individuals (1/319 + 1/1023). (Rounding: The math actually adds up to 1 in 371,608.5, which rounds to 1 in 400,000.)

In the current analysis, we established the prevalence of molecularly defined ADH at ~1:300,000 (1/407,863 for HoFH/compHeFH + 1/4,180,597 for hoFDB) inhabitants in the Netherlands, which is at least three times more frequent as previously described. The prevalence

HeFH prevalence (left) is explicitly listed as 1/319, not 1/244 (right).

Further shift in the scientific record: HeFH used to be a subset to the category heading, HeADH (left) ... and now HeFH is the whole set (right).

HoADH on the left is HoFH on the right.

(Rounding: 1/200 is from the 2013 EAS report, not the actual source; HoFH derivation therefrom is 1/160,000. But the Corrigendum to the true source was 1/223, which works out to 1 in 198,023, rounding to 1/200,000.)
The prevalence of HoFH was actually confirmed with the very same data presented as refutation.

Is there a good reason for blending different diseases under the name of one of them? Compound HeFH will soon be HoFH. What happens when we hold to the historical record, and tease the underlying components out from the new name? As with all of the FH studies that I have found, the claim of doubled, tripled, even sextupled prevalence is not only refuted by the studies’ own raw data, but the old numbers are confirmed by the very data used to claim the refutation. Prevalence for HoFH was originally said to be 1 in 1,000,000. In the Dutch study, there were 20 HoFH found. But 4 of those were said to “inflate the prevalence,” so they were explicitly removed, leaving 16 employed in off-text calculations:

1st page: Readers are misled into thinking that results are derived from 20 homozygotes.

2nd page: However, those from consanguineous parents “would inflate the prevalence.”


This key HoFH number “16” is nowhere to be found in the entire report. And this report is on the homozygous, yet a prevalence number for the true homozygous FH is not in the text. Digging into the raw data and text, true HoFH is 1/1,045,149, astonishingly close to the established number. Yet this result will not be mentioned, not here, not in the 2014 EAS. This Dutch study will blend in compound heterozygous FH and cite the total. Then the 2014 EAS will take that number and add in the HoFDB, and simply call all of these, “HoFH.”

Restoring citation and linguistic integrity is all we need to recover the underlying math.
The linguistic confusion is easily exposed through the recent Regeneron study in Pennsylvania.

Note that FH-as-LDLR is 1:518 ... still roughly the 1:500 estimated by the Nobel Prize winners. Nonetheless, this report became a jumping point for the lead author to claim on Twitter:

“FH is “twice as common as it was thought to be.” (See illustration above.)

And here is a co-author in a press release, with a nearly identical phrase.

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

['Geisinger and Regeneron study finds life-threatening genetic disorder is substantially underdiagnosed,' Dec. 22, 2016]

But FH "was thought to be" FH-as-LDLR, which was estimated to be around 1:500 to begin with, and in this study FH-as-LDLR is still around 1:500.

As for the total prevalence, the Regeneron study and our passive mathematical exercise are not yet parallel. Earlier studies of FDB only counted the R3500Q mutation and concluded a prevalence between 1:1,000 and 1:1,250.
Inflating FDB: Earlier studies only counted the R3500Q
R3500Q is also known as p.Arg3527Gln. This is the mutation used in the past when calculating FDB prevalence. There is another controversial APOB mutation often referred to as R3531C; in the Regeneron study, it is referred to as p.Arg3558Cys. In the lab p.Arg3558Cys (R3531C) shows some interference with cholesterol processing. However, in living humans, it has been said to be too weak to be included as FDB. But this controversy does not affect us here. We are in a math exercise, not a scientific effort. We are simply trying to bring two sets of mathematical tables into comparison. Since p.Arg3558Cys (R3531C) was not included in prior prevalence studies, and since it is included in this Regeneron prevalence study we can either take the p.Arg3558Cys (R3531C) out of the Regeneron study or add it into the table provided by Rader, et al. (Page 14.)
Let’s give Regeneron’s 2016 report the benefit of the doubt and assume that the heretofore uncounted \textit{p.Arg3558Cys} should be counted as FDB. To do so, we add the Regeneron study’s 1 in 1,102.7 into the established estimates as presented by Rader, et al. (We derive the 1 in 1,102.7 by referencing the Regeneron study’s Supplement: 50,726 total / 46 p.Arg3558Cys = 1,102.7.) This will bring the old and new studies into alignment and allow an \textit{apples-for-apples} comparison.

1. FH \(1,000,000 / 500 = 2,000\)
2. FDB \(1,000,000 / 1,000 = 1,000\)
3. FH3 \(1,000,000 / 2,500 = 400\)
4. \(p.Arg3558Cys\) \(1,000,000 / 1,103 = 907\) (Regeneron study.)
5. Prevalence: \(1,000,000 / 4,307 = 1:232\).

Now the old and new prevalence estimates are more parallel than they were before.

<table>
<thead>
<tr>
<th></th>
<th>Old Prevalence</th>
<th>New Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of all mutations</td>
<td>1:232</td>
<td>1:222 ~ 1:256</td>
</tr>
<tr>
<td>Prevalence of FH-as-LDLR</td>
<td>1:500</td>
<td>1:518</td>
</tr>
</tbody>
</table>

FH prevalence has \textit{not} been overthrown. The old and new numbers actually compare well:

- FH-as-LDLR was originally said by a Nobel Prize winner to have a prevalence of 1:500.
- The Regeneron study shows a prevalence of the LDLR to be 1:518.

The only thing \textit{new} here lies with linguistic usage.
Summary of conflation: Add the APOB and PCSK9 into “FH” prevalence

In the image below, on the left: in 2003, LDLR, APOB, and PCSK9 were considered Autosomal Dominant [Hypercholesterolemia] (ADH). FH is a **subset**. On the right, in 2016, the same three are called, “FH.” FH is now the **whole** set. In both papers, of course, FH-as-LDLR is the same 1:500. The different "FH" numbers between the two studies is due to linguistics, not epidemiology. Those who are working with FH are now declaring that Goldstein and Brown’s *epidemiological* estimates are obsolete and incorrect. In their stead we find *linguistics*. How do the Nobel Prize winners take this? It’s hard to say. Nobel Prize winners Goldstein and Brown have been Regeneron directors for years now. One of the authors on the Regeneron report, George Yancopoulos, is listed in Regeneron’s 10-K as President, Chief Science Officer and Director. However, one thing is not in doubt: the integrity of the scientific record has been compromised ... and such a tendency, in medicine especially, ought to concern everyone.
Fact-ectomy: How the removal of grammatical elements equivocates heretofore unequivocal usage

How this conflation took place within the scientific record is eye-opening. Unfamiliar terms create room for misunderstandings that familiar terms would never allow. So let’s first use both a familiar context and familiar terms to outline the basic linguistic mechanism at work. Think of it as a kind of “fact-ectomy” -- removing a detail, from an equation, by supplying a more general term, in the new text. When this hole in the text-body “heals” over time, the surface conclusion has moved to a new location, in this case from 1:500 to 1:200. The whole process however is only literary; the underlying population has not changed at all, only our perception of it. Next I will present a simple illustration of how this works. We will then follow up with the actual case.

<table>
<thead>
<tr>
<th>Year</th>
<th>Studies</th>
<th>Detail Added to or Dropped from the scientific record</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st report</td>
<td>Nobel prize winners Jane and John Doe make a first-of-its-kind estimation of the population of domesticated Horses in SomeCountry: 1,000,000.</td>
<td>Nothing is dropped. A discovery is added to the scientific record.</td>
</tr>
</tbody>
</table>
| 2nd report | Breakdown of prior studies under the category, Equidae:  
  - Domesticated Horses: 1,000,000  
  - Zebras: 500,000  
  - Donkeys: 250,000  
  Under the umbrella-term, Equidae, we have a total population of 1,750,000 | Nothing is dropped. A useful aggregation of prior research is added to the scientific record. |
| 3rd report | Explicit combining of the terms "Domesticated Horses," "Zebras," and "Donkeys" -- now all are called "Horses." | Use of Equidae as the umbrella-term for the constituents is dropped for an overlapping use of the word, "Horse." Although explained, ambiguous usage of "horses" is added to the scientific record, a subtraction from the clarity of the previous unambiguous usage. |
| 4th report | Implicit combining of Domesticated Horses, Zebras, and Donkeys -- all are implied to be "Horses." | The explicit reference to blending the terms is dropped, and the idea of their possible combination is only available to those who pay close grammatical attention to ambiguity. Without such attention, the assumption that "horses" are, and always have been, Zebras and Donkeys will prevail. Substantial detail is subtracted from the scientific record. Of course this is ludicrous in this familiar context, because we are familiar with the terms. Outside of a familiar vocabulary, however, the problem is more difficult to see. |
| 5th report | Now Horses are explicitly defined as Domesticated Horses, Zebras, and Donkeys. This is conflation -- and we do mean this in the linguistic sense of the term: conflation is not a "scientific" concept. | The implicit reference to the combining of separate terms is dropped. Zebras and Donkeys are now linguistically conflated with Horses. Critical detail is subtracted from the scientific record. |

Details are dropped from one publication to another, and this allows a "conclusion drift" from the specific definition of domesticated horses to a general, stretched definition of "Horses." Due to successful conflation, recent scientists declare that the estimates of the Nobel Prize winners fail to compare with the "new prevalence" of 1,750,000 horses. Even though the constituent of domesticated horses within that 1,750,000 is still 1,000,000.
Now let’s consider "conclusion drift" as it applies to FH

<table>
<thead>
<tr>
<th>Year</th>
<th>Added</th>
<th>Dropped</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973:</td>
<td>LDLR = FH with prevalence of 1:500 ~ 1:1,000</td>
<td>Nothing is dropped. Groundbreaking work is added to the scientific record.</td>
</tr>
<tr>
<td></td>
<td><strong>Breakdown of recent discoveries under the general category, ADH:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- LDLR = FH 1:500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- APOB = FDB 1:1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PCSK9 = FH3 1:2,500</td>
<td></td>
</tr>
<tr>
<td>2003:</td>
<td><strong>Explicit combining of the terms FH, FDB and FH3 as “FH”</strong></td>
<td></td>
</tr>
<tr>
<td>Rader et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doi:10.1172/JCI200318925</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011:</td>
<td><strong>Explicit combining of the terms FH, FDB and FH3 as “FH”</strong></td>
<td><strong>Use of ADH as the umbrella-term for the constituents FH, FDB and FH3 is dropped. A degree of clarity is subtracted from the scientific record as ambiguity is added: cultural use of FH is acknowledged to refer exclusively to the LDLR, but is not here restricted to the LDLR.</strong></td>
</tr>
<tr>
<td>&quot;Although the term FH has, in the past, been used to refer specifically to LDL receptor (LDLR) defects, this document will use a broader definition to reflect discoveries of defects in the genes for apolipoprotein (Apo) B, proprotein convertase subtilisin/kexin type 9 (PCSK9),&quot; Goldberg, et al. DOI:10.1016/j.jacl.2011.03.001</td>
<td></td>
<td></td>
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<tr>
<td>2012:</td>
<td><strong>Implicit combining of LDLR, APOB, and PCSK9 mutations. They are adjacent to the name FH, and the names for FDB and FH3 are not mentioned, leaving room for the assumption that the APOB and PCSK9 carriers are FH patients.</strong></td>
<td><strong>Gone are the references to FDB and FH3. The constituents appear next to each other spatially. However, grammatically their &quot;conflation&quot; is not necessarily true. An easy-to-make assumption due to sequential sentences, however vulnerable a reader may be, does not make an airtight conclusion. The period crucially separates the two sentences, and the word “primarily,” although suggestive, leaves us with declaring an adverb to be our smoking gun. But we can say that the explicit reference to an expanded definition of FH is dropped from the scientific record. Newcomers to FH will accustom themselves to a new definition and most likely will not even be aware of the ambiguity, especially as this “new research” replaces the old.</strong></td>
</tr>
<tr>
<td>&quot;FH is an autosomal dominantly inherited disorder caused primarily by mutations in the gene encoding the low-density lipoprotein (LDL) receptor, LDLR. Less frequent mutations in the APOB and PCSK9 genes have similar functional consequences.&quot; Benn, et al. DOI:10.1210/jc.2012-1563</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013:</td>
<td><strong>Implicit combining of LDLR, APOB, and PCSK9. For a genetically inherited disease, in a prevalence study which compares the results to FH-as-Only-LDLR, this is conflation — and we mean linguistics. Now, with the aid of the new definition for “FH,” prevalence in a Danish population is cited as 1:200.</strong></td>
<td>The implicit reference to the combining of separate terms is dropped from the scientific record.</td>
</tr>
<tr>
<td>report by Nordestgaard, et al.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Heterozygous FH is caused either by heterozygous loss-of-function mutations in LDLR, heterozygous mutations in APOB that affect the LDL receptor binding domain of apolipoprotein B, or heterozygous gain-of-function mutations in PCSK9.&quot; (doi:10.1093/eurheartj/eht2732016)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
From 2011 to 2013, critical detail has been subtracted from the scientific record, enabling a "conclusion drift" from a specific to a general use of "FH." Now in 2016 FH is said to be between 1:222 and 1:256 in the Regeneron report. And this is compared to the Nobel Prize winners' estimate of 1:500, where in the new studies, after linguistic and citation integrity is restored, FH-as-LDLR is still **1:500**.

Again, what if professor A did a first-of-its-kind prevalence study of domesticated horses, and an experienced and prominent professor B did the same, but included zebras as if they were “horses”? If professor B does not explain the conflation of “zebras” with “horses” and claims that his prevalence result is higher than professor A's, then he uses the omission of information to deceive his readers. For new students, professor B's research precedes and precludes awareness of the conflation. Now what if professor B uses his numbers to declare professor A's work to be incorrect and obsolete?

"Most physicians believe that FH is rare and not often seen in practice. In fact, it is significantly more common than 1:500, the estimate made at the time that Brown and Goldstein identified the LDL receptor. Current studies suggest a prevalence of 1 in 200 to 300 people based on work in the Netherlands, Denmark, and other countries where genetic testing has played a significant role."~ DOI: 10.1161/CIRCULATIONAHA.116.021673

The above passage was written by Anne Goldberg and Samuel Gidding and is aptly titled, "Knowing the Prevalence of Familial Hypercholesterolemia Matters." After we are familiar with the terms, the problem is rendered conspicuous. Two sentences suffice:

1. "Brown and Goldstein identified the LDL receptor" ... and its prevalence was estimated to be 1:500.
2. "Current studies suggest a prevalence of 1 in 200 to 300 people" ... **if we stretch the definition of "FH" to add FDB-APOB and FH3-PCSK9 to FH-LDLR.**

Now, in June 2018, Dr Goldberg updates the Merck Manual, returning to the old definition of FH. FH is again identified solely by the presence of the LDLR mutation. The APOB and PCSK9 are listed immediately below in their own categories – **while the Merck Manual keeps the quantities of the APOB and PCSK9 in the math for the LDLR, the “FH”: 1/200.**

| June 2018 update of the Merck Manual | “FH” returns to its original usage and is defined again solely by presence of LDLR. The APOB and PCSK9 are listed separately again. | But the APOB and PCSK9 are still included in the math. FH as solely LDLR cannot possibly be 1/200. |
Summary of the 2018 Merck Manual Update

My analysis of the linguistic manipulation is summed up with the following mathematical certainty:

- Where mutations LDLR, APOB, PCSK9, and p.Arg3558Cys are each greater than zero, LDLR alone cannot equal LDLR + APOB + PCSK9 + p.Arg3558Cys.

But the bad math, where LDLR does equal LDLR + APOB + PCSK9 + p.Arg3558Cys, has prevailed. Here is the logic leading up to the recent June 2018 “update” found in the Merck Manual.

The Chronology of the Mathematical Fracture in the Merck Manual’s FH Prevalence:

1. In 2003 Daniel Rader explicitly defines FH, FDB, and FH3 according to the scientific record thus far, that is, separately, and with their respective prevalence rates.
2. In 2007 Daniel Rader receives over 250,000 shares from Aegeri Pharmaceuticals, Inc.
3. In 2011 Dr. Anne Goldberg and Dr. Daniel Rader co-author documents which explicitly combine APOB and PCSK9 with LDLR and declare a higher prevalence for a new version of “FH”: 1/300. No citations are provided that justify this number. However, with casual addition, LDLR + APOB + PCSK9 = 1:300 (rounded from 1/294). The names “FDB” and “FH3” are dropped from future, pharma-dominating FH papers.
4. In 2012 the 1st Danish report furthers the conflation scheme and, after several shenanigans, FH is 1/200.
5. In 2016 the 2nd Danish report conflates names, adding data which exposes a patient swap. (I will cover this swap in a separate presentation.) FH is again said to be 1/200. Through my analysis and the removal of an inflated denominator, FH-as-LDLR is confirmed to be 1/500.
6. In 2016 Regeneron adds in the controversial p.Arg3558Cys mutation. Now “FH” equals LDLR + APOB + PCSK9 + p.Arg3558Cys, without explanation. FH prevalence is now said to be 1 in ~250. Using the study’s own data, the prevalence of the originally defined FH – FH-as-LDLR – is confirmed to be 1/500 after linguistic integrity is restored.
7. In 2018 Dr. Goldberg updates the Merck Manual. This is a disease manual and not an “FH” manual and so Dr. Goldberg must list all of the related diseases. The new version of “FH” must be linguistically “unpacked” back into the old categories once occupied by the APOB (“FDB”) and PCSK9 (“FH3”). Without the linguistic manipulation, the Danish and Regeneron reports confirm FH-as-LDLR to be 1/500. Without the 2011 conflation by Dr. Goldberg, FH prevalence is 1/500. So why is 1/200 used for FH-as-LDLR in the Merck Manual? By “unpacking” FH back into the pre-2011 categories, linguistically, FH is here once again exclusively defined by the LDLR, while FDB is listed immediately below – defined and counted separately by the presence of the APOB mutation. Nonetheless, FH-as-LDLR keeps the FDB-as-APOB and other disease quantities combined into the total.
8. Thus, the equation behind FH prevalence in the Merck Manual, exposed by the historical record, is mathematically impossible LDLR = LDLR + APOB + PCSK9 + p.Arg3558Cys.

### Underlying Cause

<table>
<thead>
<tr>
<th>Underlying Cause</th>
<th>Disease Name</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>“FH”</td>
<td>1/500</td>
</tr>
<tr>
<td>APOB</td>
<td>“FDB”</td>
<td>1/1,000</td>
</tr>
<tr>
<td>PCSK9</td>
<td>“FH3”</td>
<td>1/2,500</td>
</tr>
<tr>
<td>p.Arg3558Cys (R3531C)</td>
<td>(Controversial inclusion)</td>
<td>1/1,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>All now called “FH”</td>
<td>1/227</td>
</tr>
</tbody>
</table>
The contradiction in the 2018 update of the Merck Manual

The 2011 article spearheaded by Dr. Anne C. Goldberg was a pivotal moment. Dr. Goldberg was the lead author in the declaration that the APOB and the PCSK9 mutations would thenceforward be included in the definition of “FH,” and by implication, would no longer be associated with the names “FDB” or “FH3.” Mention of the blending of names was dropped thereafter in pharma-funded publications. Today it almost appears as if this linguistic event never happened. Whatever reason there may have been for the conflation is refuted by Dr. Goldberg’s contributions to the 2018 Merck Manual update. FH prevalence is now 1:200. But FH is defined by the presence of the LDLR mutation alone. APOB and PCSK9 mutations are excluded from the definition. APOB and PCSK9 are listed immediately below on separate rows, designating separate diseases. In short, the Merck Manual keeps the inflated math, while teasing the three names back out, linguistically, and listing the diseases and their causes separately again. Why do this?

How is this possible? This is the Merck Manual, not an “FH manual.” Not everyone visits this page to read about FH. Readers need to see all of the lipid diseases separately. This presents a problem: either the prevalence of the LDLR must return to 1:500 or the APOB and PCSK9 mutations must be double counted. The lead author of the 2011 series and the expert who updated the 2018 Merck Manual are one and the same, Dr. Goldberg. We arrived at 1:200 largely by adding LDLR + APOB + PCSK9, but now LDLR alone is 1:200. It’s impossible; in an equation, LDLR = LDLR + APOB + PCSK9.
This conflation is also present from the 1st Danish report to the 2016 Regeneron report. We can use any of them for comparison. Let’s put Regeneron’s report next to the Merck Manual, 2018.

- If there was any doubt as to whether the 2011 linguistic conflation took place in good faith, it is here refuted: in unpacking Dr. Goldberg’s earlier linguistic blending of terms, the underlying math should also have been unpacked.

A doctor must trust the experts ... who are they? What’s the source for FH prevalence here? For diagnostic procedures? For treatments? The 1/200 number in the 2018 Merck Manual is most likely from the 2012 or 2016 Danish reports, led by Dr. Marianne Benn. The Merck Manual replied to my request for source material for the FH prevalence number in Dr Goldberg’s June 2018 Merck Manual article.
Dr. Goldberg was the lead author in the 2011 Aegerion-sponsored publication that helped push the linguistic conflation into motion. Dr. Goldberg is even an author of a piece in the American Heart Association’s “Circulation” titled, “Knowing the Prevalence of Familial Hypercholesterolemia Matters.” However, there are so many financial interests at work around FH issues and associated specifically with the original 2011 paper that it is difficult to tease out a clear line of influence. But Merck’s footprint is here along with the others. Merck Manual’s “Editorial Independence” is questionable.

DOI: 10.1161/CIRCULATIONAHA.116.021673
Although they eventually abandoned it, Merck had high hopes for anacetrapib as a treatment for FH, including the years 2011 through late 2017.

From the time of Goldberg’s 2011 article and through the years to the present, Merck and Merck’s investors have a financial interest in the prevalence of Familial Hypercholesterolemia. Products marketed in this space include Zetia, Zocor, and Vytorin.

https://www.sec.gov/Archives/edgar/data/310158/000119312512084319/d274705d10k.htm

Comparisons: Amgen then and Amgen now; Amgen now and Regeneron now

Here’s another recent event where pharma players find themselves boxed in by the success of their own scheme. Let’s use the framework provided by Dr. Goldberg’s Merck Manual entry as background to a legal problem. Note that the Merck Manual listing breaks down the diseases within the heading, “Dyslipidemia (Hyperlipidemia).” Then the article breaks down the category, dyslipidemia/hyperlipidemia, into subcategories Primary and Secondary. “Primary” refers to genetic causes and “Secondary,” to “lifestyle and other factors.” The next category down (the “sub-subcategory,” if you will) lists the different diseases, FH and what were formerly known as “FDB” (APOB) and “FH3” (PCSK9). Familial Combined Hyperlipidemia (“FCH”) is also here … along with several other diseases.

Now here’s the confusion. When Amgen first applied for FDA approval for its drug Repatha, it requested that the drug be available to patients with primary hyperlipidemia. This was rejected. It was however approved for a subcategory, the heterozygous form of FH. (For this discussion, we’ll set aside the CardioVascular Disease [CVD] component of the indications. I’ve limited my analysis to the FH portion.) Without the prior linguistic manipulation, this clear rejection, de jure, would have excluded the FDB, the FH3, the FCH, and the others. But the pre-FDA linguistic maneuver14 did take place and the FDB and FH3 were effectively redefined as “FH,” and so, de facto, the FDB and FH3 were “included” in the FDA’s approval … but not FCH. FCH was not part of the linguistic maneuver. So legally, what would be the difference between Amgen’s inconspicuous promotions for FDB sales and a hypothetical, conspicuous attempt at FCH sales? Is an FH promotion that silently includes those formerly defined separately as FDB on-label? Would an explicit “FDB” promotion still be on-label? If yes, then would promotion of FH-indicated drugs to the FCH be on-label or off-label promotion? The line has been blurred through deliberate, scientific obfuscation, and the increased market for FH drugs is made up of this linguistically manufactured grey area. How is this question even possible if the FDA is the ultimate authority? Who really decides what underlies an FDA drug indication?

Now as it turns out the indication for Amgen’s drug has expanded to include, not just FH, but now Primary Hyperlipidemia as a group.15 So what? For example, imagine I arrive at a fruit stand and when the vendor is not looking, I secretly place apples under oranges within a box labeled, “oranges.” I next offer $5 for all the fruit on the table. Why not? What have I got to lose? If he says, “No, but you can have that box of oranges for $5.” I grab the box of oranges – and with it, the apples I have previously slipped in. Is it a legal purchase just because I get away with it? If I somehow manage to convince myself that it was legal yesterday, what do I do if the vendor then explicitly makes a new offer, “I’ve got a better deal for you today. I’ll give you both the oranges and the apples together for the same $5.” If it had already been legal and aboveboard yesterday, what has just happened today? If legal, what basis would there be for considering this to be a new deal? What reason would I have to be pleased with the offer? If it is not a new deal, why would the vendor say anything at all?

14 The conflation begins at least as early as 2011.
15 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125522s014lbl.pdf
1. If I explicitly acknowledge that a **new and better** deal has been made, I imply a difference from the previous deal.
2. **What is that difference?**
3. **The vendor did not intend for me to take the apples yesterday.**

The very fact that the vendor makes the new $5 offer tells me that I was **never** offered the apples the first time. Acknowledging the fact that there is a **new** deal, I also acknowledge that I simply **stole** apples in the last deal.

If the FDA tells Amgen that they can now market to all those with primary hyperlipidemia, as opposed to the previous indication which restricted them to FH, was it previously legal to market to the other members of primary hyperlipidemia, FDB and FH3? Has anything changed at all? (The emphasis here and in the passages that follow are 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).** ~ Vrablík

That was in the year 2000. How far have we travelled? Just a short while ago, pre-2011, calling the APOB mutation carriers “FH” instead of “FDB” was outright misdiagnosis. Now no one is the wiser. But FCH? That would be going too far evidently. Note that the reason why only 3-5% of the FDB patients are incorrectly diagnosed is because FDB is much milder than FH. Most don’t pass the industry’s recommended circumstantial scoring system. Vrablík continues,

> 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). ~ Ibid.

So FDB and FH are known to have very different degrees of severity. A demarcation between types of diseases has an increased medical value. Does this demarcation increase or decrease the financial value of a stock trading on Wall Street? Precision limits the range of targets, but expansion **resists** limits, resisting precision in the consequence. **Precision is important to disease identification, imprecision to marketing expansion** – in which of these directions do we travel when we conflate FDB with FH? Who decides? Pharma puts practicing doctors on a “need to know basis.” Below, pre-2011 (2008), FH and FDB are clearly two separate diseases. Again, they also involve **two different degrees of severity.**

**Familial hypercholesterolemia (FH) and familial defective apoB 100 (FDB) are characterized** by increased plasma low-density **lipoprotein** cholesterol (LDLc) levels and risk of **coronary heart disease** (CHD). FDB is clinically indistinguishable from FH. **FDB lipoprotein phenotype was significantly less severe than that observed in FH carriers of LDLR gene missense ligand-binding domain mutations.** ~ Ejarque

Have doctor’s been put on a need-to-know basis?

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16 “Major Apolipoprotein B-100 Mutations in Lipoprotein Metabolism and Atherosclerosis,” 2000, M. VRABLÍK, R. ČE.KA, A. HOŘÍNEK

17 Also, note that the 1998 citation in the above refers to some of the same authors of the Danish reports. They will change their minds and eliminate this observation, after pharma-funding.

Shouldn’t differing degrees of severity, not to mention differing disease mechanisms, merit a doctor’s specific awareness? Why would the historical record be altered to the point that it serves more as an eye patch for the doctor than additional light on the patient? If altering the scientific record for profit is above the law, then there is no limit to the damage that pharma can do.

Here is a paper published in 2018.

Recently homozygous FDB patients were identified. Hypercholesterolemia was less severe in these subjects than in patients homozygous for FH, in which the LDL receptor is defective. “Schaefer”

The message is the same. FH and FDB are two different diseases, with different mechanisms, and crucially, with different degrees of severity. It is not just the recent push for “precision medicine” but just plain common sense that tells us that genuine medical practice opts for preserving detail and not removing it from the scientific record. If Big Pharma can re-define diseases through a publication strategy, removing detail and creating grey areas to capture more sales, pre-FDA approval, then both the FDA and the practicing physicians remain on a “need to know basis,” where the “need” is profit … a profit threatened by a doctor’s improved vision. By controlling medical instructions, the manipulation subordinates the role of the physician to that of pharma’s full profit potential.

With the weakened diagnostic scoring systems in place, and genetic testing downplayed, all those who merely share characteristics with genetic FH are effectively renamed “FH.” This captures a significant number of those with merely secondary hyperlipidemia. However, for argument’s sake and for the present purpose, let’s just talk about Primary Hyperlipidemia and the FDA indications.

With FH, a definition of specific genetic inheritance met a specific FDA indication, while the prevailing literature had already slipped out of its genetic constraints as the disease name stretched over a broader range of conditions. Genetic-based medicine is touted as “precision medicine” and FH is supposed to be caused by a

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19 Homozygous Familial Defective Apolipoprotein B-100: Enhanced Removal of Apolipoprotein E–Containing VLDLs and Decreased Production of LDLs, 2018, Shaefer, Scharnagle, et al. [https://www.ahajournals.org/doi/abs/10.1161/atvb.17.2.348](https://www.ahajournals.org/doi/abs/10.1161/atvb.17.2.348)
narrowly defined genetic inheritance. Science and medicine pursue ever finer detail in the pursuit of precision, but the marketing here thrives on obscurantism, a wide shadow cast over neighboring definitions. How far and wide this shadow prevails depends upon limiting its extension just short of becoming conspicuous.

As far as FDB and FH3 are concerned, what has changed with Amgen’s new indication? With Goldberg, et al’s, linguistic maneuver, the expanded indication is a fait accompli – no one is the wiser. FH has become FDB and FH3 ... but not FCH? FCH, in fact, is on some publications’ “exclusionary criteria” – IE, it is regarded as misdiagnosis to take the FCH for FH, just as it was once regarded as misdiagnosis to include the FDB as FH. Why not also confine the FCH? I’ll speculate a little here. First FCH is the most common of the genetically caused dyslipidemias, with a prevalence between 1/50 and 1/100. The resulting inflation of FH prevalence would be very conspicuous. Second, FCH was described by the same Nobel Prize winner in the 1973 publication which is often cited for the prevalence of FH. In short, FDB and FH3 are still new and relatively unknown. FCH, on the other hand, was widely publicized alongside FH – 45 years ago; it is easier to manipulate information regarding lesser known, newer diseases which are not yet entrenched in textbooks or among older, experienced physicians.

But setting aside that speculation, what matters in the present argument is the fact that there is a heading called Primary Hyperlipidemia. Sometimes FDB, FH, and FH3 had their own heading assigned, “Autosomal Dominant Hypercholesterolemia.” However, regardless of the category heading used on a given occasion, FH, FDB, FH3, FCH, were once distinct mathematical sets,” each demarcated, separated and categorized with an equal rank within a given literature and disease hierarchy. Then an organized, orchestrated, Pharma-funded linguistic conflation of the diseases took place.

We can also see Amgen’s linguistic-legal confusion when we bring in Regeneron’s current indication for its drug, Praluent. When Amgen’s changed indication is set next to Regeneron’s current indication, is there a legal difference? Regeneron’s drug is restricted to the subcategory, HeFH; Amgen, is now able to promote to the whole category, Primary Hyperlipidemia, which not only includes HeFH, but FDB and FCH. If Amgen is only now permitted by the new indication to include the APOB and PCSK9 carriers, is Regeneron forbidden to do the same without an indication for Primary Hyperlipidemia? If so, was it legal for Amgen to promote to such before the indication change? If permitted, why wouldn’t Regeneron be able to promote to FCH as well?

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21 https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=446f6b5c-0dd4-44ff-9bc2-c2b41f2806b4
Who is in control if Big Pharma is allowed to cherry-pick and fund authors willing to go along with a language strategy and completely redefine diseases before they reach FDA consideration? Big pharma is.

Established prevalence, Rader, et al.

Monogenic hypercholesterolemia: new insights in pathogenesis and treatment

Table 1. Regenene hypercholesterolemic diseases that cause severe hypercholesterolemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defective gene</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>LDLR</td>
<td>1/1000</td>
</tr>
<tr>
<td>FDB</td>
<td>APOB</td>
<td>1/1000</td>
</tr>
<tr>
<td>FH3</td>
<td>PCSK9</td>
<td>1/1000</td>
</tr>
</tbody>
</table>

The established prevalence is actually confirmed, not overthrown.

Before recent publications, those with APOB mutations were defined as FDB. Those with PCSK9 were FH3.

Recent PR for the Regeneron report claims that FH is “twice as common as it was thought to be.” But this is a cultural, linguistic conflation of FDB and FH3 with “FH.”

The linguistic conflation of established rates for the separate diseases requires a passive mathematical adjustment, with roughly the same result as found in Regeneron’s.

The Regeneron report included a controversial APOB mutation, a very mild form in who which had been excluded in previous FDB prevalence studies: p.Arg3588Cys.

Regeneron’s indication is the same as Amgen’s was before.

As far as FDB and FH3 are concerned, what legal right has Amgen been granted that Regeneron is not already taking? As for the industry’s recommended scoring system, even FCH and others will be mixed in.

Amgen reapplied for a new indication. Its Repatha is now approved for Primary Hyperlipidemia. If the FDA had been the law, then FDB and FH3 would only now be added, but they had already been renamed, “FH,” in pharma-funded publications.

Changed” to the whole category...

There is no effective difference with FDB and FH3. The FDA indication is just paper.

• Before recent publications, traditional FH referred to LDLR and had a prevalence of 1:500.
• Now, FH-as-LDLR is still around 1:500.
• (50,726/98 = 518)
• Is 1:222 a doubled prevalence within epidemiology or a linguistic issue?

http://dx.doi.org/10.1126/science.aaf7000

DOI:10.1126/science.aaf7000

The Regeneron prevalence results

A

B

Netherlands (8) "Diagnosis of FH prevalence is a US health care system-wide problem. This study supports the claim that there is a gross under-diagnosis of this condition in US.

WHO CENTRES

Undifferentiated

Genetic identification of familial hypercholesterolemia within a single U.S. health care system

Password: [redacted]

Participants recruited from various centers related to the study

Participants recruited from centres of collaboration

Population characteristics

Frequency

Prevalence

1:1200

1:300

1:100

1:20

1:2

1:500
There are many issues here, but this portion of my analysis is concerned with mostly one

If the FDA is going to approve a drug for "FH," how many drugs would be sold ... with this new definition? ... or that old definition? If the APOB mutations are milder than the LDLR, do they both share the same risk-benefit profile in regard to risky treatments? For investors, what is the addressable market?

All these are important questions. But first things first. The issue of whether to include or exclude FDB under the definition of "FH" is an issue for the medical community and the FDA to decide. I'm not saying that such is not important. It is. However, we are doing something more elementary here: we are trying to compare apples with apples, and not apples with oranges. The violation I outline here is with simple linguistics and math. Stretching the definition of FH over FDB and FH3 and controversial p.Arg3558Cys and then setting the result alongside previous studies that did not stretch the definition must be accompanied by both a detailed explanation and a routine breakdown of the mathematical adjustment.

In another way of looking at this, FH-as-LDLR+FDB+FH3 is indeed an increase over FH-as-LDLR-alone. Likewise, a whole pie is larger than one of its slices. If this is to be more than a meaningless truism, some explanation would be useful here. Perhaps we could use a map of the differing FH definitions, where readers could zoom in and out of the different dimensions afforded by phenotypic versus genotypic perspectives, and the differing clinical scores of their constituents. Who is included with one definition but excluded with another? This might be useful as an exercise in clarification. But there is no legitimate prevalence comparison here. For a prevalence comparison to take place, the types which actually underlie the sets must first be identical. As it is, we are really comparing linguistic usage.

With this publication strategy, science-based predictions win and fail

The prevalence of LDL receptors estimated by Nobel Prize winners, Goldstein and Brown, was risky. We can see however that the new numbers provided by the Regeneron study supported Goldstein and Brown's estimate. This should be pretty big news.

Imagine when Einstein's theory demanded that light from a particular star would not travel in a straight line because of the Sun's gravity. It was pointed out that this bending of light could be proven during a solar eclipse. This event presented an enormous risk for Einstein's theory and reputation. When the time came, the light behaved precisely as Einstein's theory said it would, and to his well-deserved acclaim.

Imagine however that his theory had not been so famous. Imagine a culture that did not respect the scientific record. Imagine that someone else renamed the whole event and altered its interpretation of the theory in his own favor. Now imagine the same event takes place, supporting Einstein's daring idea, but because culture has been retaught a different language, and a redefined set of terms, Einstein's prediction is considered obsolete and even incorrect -- precisely when events actually lend it the strongest support to date.

This is pretty much what is happening with the Nobel Prize winners' definition of FH and their prevalence estimate. The verification of their estimate should have been big news. But it wasn't. Precisely when their numbers were supported by new evidence, their numbers were said to be wrong -- by that same evidence.

Now the two Nobel Prize winners are on Regeneron's board.

Using linguistic conflation to claim that the same, old data is somehow different, updated data

Recent publications are using linguistic conflation to claim and "prove" that Goldstein and Brown's original estimate is mere "dogma."
In the above presentation at the FH Foundation -- whose topic was the history of FH prevalence -- the original 1:500 was said to be from a "Joe Goldstein." There was no mention of him as Joseph Goldstein, Nobel Prize winner -- and co-discoverer of the LDL receptor. The entire backdrop to the presentation is more or less: the old dogma has fallen to new examinations and discoveries. And this is pretty much the refrain of countless new studies of FH prevalence: "The established rate is X-number, but new studies show Y-number." As if 1:500 was a former belief, overthrown by new evidence. But has the old FH-as-LDLR estimate really changed within epidemiological discipline? It is very clear that when the constituents of the new prevalence studies are broken down that the numbers match up pretty well with the Nobel Winners' estimates.

Mismanagement of the scientific record spanning separate publications is, for whatever reason, partly to blame. Through a series of scientific papers, instead of pursuing specifics and maintaining a parallel perspective with their targets of criticism, specifics are dropped .... and this allows a "conclusion drift" toward generalization and a blending of names. Different populations are added to a single name, and this aggregation is presented as if an "increase" over one of its constituents. Once our research chases down all the terms, this "epidemiology" is as much of a truism as it is to say that the whole pie is bigger than one of its slices.
Summary of conflation: Add the APOB and others to “FH” prevalence

The illustration below shows the consequences of citation kiting -- as if they were "Before" and "After" photos. The 2003 "Rader report" and the 2016 "Regeneron report" expose the linguistic and mathematical "conclusion drift" that took place in the interim. So here is the gap between the former unequivocal usage of “FH” and the new equivocated version. In the image below, on the left: in 2003, LDLR, APOB, and PCSK9 were considered Autosomal Dominant [Hypercholesterolemia] (ADH). In both papers, FH-as-LDLR is the same 1:500. Now, however, the Regeneron report tells the world that prevalence used to be “1:500,” but now it is “~1:250.” But 1 in ~250 mostly represents the old category heading, ADH – not the prevalence of the LDLR gene, which used to go by the acronym, “FH.” Now, all three are the “FH gene.”

![Image showing the difference between the 2003 and 2016 reports on FH prevalence]

2003: Established prevalence, DOI:10.1127/JCI200318925

2016: “New” prevalence results, DOI:10.1126/science.aaf7000

**ADH as the entire Set**

**FH as a Subset: LDLR**

FH as the entire set

FH-as-LDLR prevalence is unchanged.

50,726/98 = 1:518
The different "FH" numbers between the two studies is due to linguistics, not epidemiology. Nobel Prize winners, Goldstein and Brown, have been directors of Regeneron for years now. Nonetheless, the reverence due the scientific record has been flouted, without anyone in the medical community stepping up. Such vulnerability, in medicine especially, ought to concern everyone.
After using the APOB for ‘underdiagnosis’ the recommended diagnostic scoring systems abandon them.

So what’s the big deal? What does it matter if we count 1:250 FH with APOB or 1:500 FH without APOB? That old 1 in 500 “dogma” didn’t include the new information about the recently discovered APOB. Now we know better. Isn’t that progress? And by calling all of them by the better-known, “FH,” instead of the relatively unknown, “ADH,” can’t we now say, albeit tongue-in-cheek, that we have “twice” the number previously used for “FH” prevalence? Don’t we perform a service by increasing the decibels of the alarm, “Underdiagnosis!”

It matters because it doesn’t matter. These very authors tell us so by abandoning the APOB in their next step. After all this effort to re-engineer the name “Familial Hypercholesterolemia” to include the APOB, these APOB are abandoned by the diagnostic procedure recommended by the very same authors … in the very same publications. It all makes sense if … the APOB carriers are used for advertising “underdiagnosis” but are no longer necessary at the point of diagnosis – the point in the medical process where prescriptions are sold. The authors’ concern and sympathy for the APOB is fully depleted in the effort to elicit our concern and sympathy, and there’s none left by the time the authors’ get to recommending the actual diagnostic system.

Any move away from clarity and precision and toward obfuscation and imprecision should be sufficient reason for condemning the equivocation of terms within the scientific record. And the real injuries do not stop with mere publications and linguistic distortion: real people are at the other end of diagnostic procedures.

- Whatever reason there is for including the APOB in “FH” prevalence refutes excluding them in the recommended diagnostic procedure.
- Whatever reason there is for excluding the APOB from diagnosis refutes the medical necessity of including them in claims of “underdiagnosis.”

Here is the 2nd Danish report, 2016.
Without the infrastructure, education, and profit motive for widespread genetic testing, 95% of the APOB will not be counted as “FH” when using the recommended scoring system. Here, 105 out of 111 would have been left out. The APOB are emphasized when it comes to academically determined prevalence, which leverages the advertising message, “underdiagnosis,” but then when it comes to real-world diagnosis, the clinical prejudice of what FH should look-like would have passed these over undetected. When an insurance policy is restricted to Definite FH, 100% — all APOB — would have been abandoned in a real-world clinical setting. After the APOB entrance for prevalence they are spun right back out of the real-world clinic as if in a revolving door.

So what does it really matter if we conflate or don’t conflate diseases? What’s the big deal? This feels like a bait and switch scheme, executed from behind the institution of peer review. Whatever reason authors have for saving the APOB when talking about prevalence is not satisfied by discarding them when selling their drugs.

The APOB journey from Prevalence to Recommended Diagnosis

- Originally, FH-as-LDLR
- Now, FH-as-LDLR+APOB
- FH-as-passing-clinical score excludes APOB

Step 1(a): Conflate “FDB” (APOB) with “FH” (LDLR). 1(b): Use genetic matching for the prevalence count, proving the urgency of “underdiagnosis!”

Step 2: The recommended diagnostic procedure, operating in the real world, swaps the APOB back out, guaranteeing their underdiagnosis.
A rational demonstration: It’s all about the money and healthcare is in the way

Everyone is complaining about a so-called “broken” healthcare system. But what they fail to mention is the resilience and strength of wealth-care in America. How does this argument sound? For reason X, the underdiagnosis of APOB demands a diagnostic procedure that abandons these underdiagnosed APOB. What could reason X be? Why conflate the APOB with the LDLR for “FH” prevalence only to leave them out with the recommended diagnostic procedure? Is this an exercise in futility? Or does it serve some function?

The industry has two simultaneous interests, healthcare and making more money. In a conflict, one of the two will dominate. For these industry-funded publications, which is it? A balanced debate in a scientific discussion or an unbalanced push toward more money?

➢ It can be rationally demonstrated that Big Pharma’s predicament is solved by sacrificing healthcare as the primary concern.

1) Step 1, Zig: The prevalence study goes against history to include the APOB as “FH” for reason X.
2) Step 2, Zag: The diagnostic procedure identifies individuals for drug sales, but it goes against the effort of Step 1 and suddenly excludes the APOB for reason Y.
3) Reason X can and cannot equal reason Y, depending upon what is referred to.
4) To remain consistent, reason X cannot equal reason Y if either X or Y refers to the health and welfare of the APOB. Under normal, fully disclosed circumstances …
   a) … if the APOB are included in prevalence for their well-being, then their exclusion at the diagnostic stage is against their well-being.
   b) … if the APOB are excluded at the diagnostic stage for their well-being, then their inclusion in prevalence cannot have been for their well-being.
5) To remain consistent, reason X can equal reason Y if both refer to making more money, within which Prevalence and Diagnosis are successive steps necessary to a bait-and-switch procedure: the inconsistency is the engine, not the obstacle.
Most of the LDLR are also abandoned.

The problem is not limited to the FDB-APOB carriers, but “classic” FH-LDLR carriers are also left behind. In the 2nd report, 70% of the 3 most frequent LDLR would not pass the clinical scoring system, assuming the industry succeeds in discouraging widespread genetic testing. With the FDB APOB and the three most frequent FH LDLR combined, 86% are abandoned when the recommended diagnostic scoring system is considered sufficient.

The Regeneron report employs the same gimmick but was more thorough.

It did not limit itself to the three most frequent LDLR. And yet the Regeneron report also recommends clinical scoring systems as if they were sufficient to determine FH. 76% of 215 carriers were below clinical detection. (Emphasis is mine, here and throughout my report)

“A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network (DLCN), Simon Broome, or Make Early Diagnosis to Prevent Early Death (MEDPED). These diagnostic tools estimate the likelihood of FH on the basis of clinical features and, in the case of DLCN and Simon Broome criteria, also include identification of functional variants in the LDLR, APOB, or PCSK9 genes. However genetic testing for these variants is uncommon in clinical practice in the United States.” ~ Regeneron report

It is easy to see here that given the discouragement and unavailability of widespread genetic testing both the APOB and the LDLR are abandoned with the recommended diagnostic procedure: the clinical scoring systems. Once a reader stops and stares at the material long enough, the eyes adjust to the dark: not only is there a reversal of the APOB, but even the original LDLR are also abandoned at the diagnostic stage. How could this happen? What’s missing from the scientific record? If something is missing can these Pharma-funded reports be balanced presentations with responsible recommendations?
Most mutations are actually milder than previously thought. The Pharma-funded reports are consistently unbalanced: the consequences of most mutations, especially the APOB, are not as severe as Pharma-funded reports claim. This good news for most mutation carriers presents a big problem for industry profits: Do most of the FH mutation carriers even need these risky new drugs?

In the 2nd Danish report, 38% of the LDLR and APOB had scores just like everyone else, deemed “unlikely” to have FH. As for the chance of having a passing score, 86% would not set off clinical alarm bells.

That deserves emphasis: contrary to the message of the industry, many of these “FH” are not as severe as they are said to be. It may be the best strategy to monitor these mild LDLR and APOB carriers ... the majority ... to inform them of their risks ... to remain vigilant, but not to jump to conclusions too soon. It certainly does appear, and many scientists have said, that environmental factors do play a role. These carriers are not necessarily doomed if they don’t pay for Pharma’s expensive, risky drugs.

“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.”

“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.”

The emphasis on the mildness of the mutations for most carriers has been snipped out of the historical record. Just as we see with the issue of genetic testing, once again there is a peripheral mention of a central issue. Somehow, critical premises do not factor into the conclusions, at all. The fact that mutations are milder illustrates how the linguistic conflation of diseases is largely irrelevant to the actual treatment of mutation carriers.

However, the fact of mildness is also a fatal premise within a complete argument for the recommended diagnostic procedure. Once this premise is retrieved from the historical record, and re-inserted into today’s record, the recommendation cannot survive. In Part 2, I will demonstrate, with Euclidean precision, a swap of “FH” populations.

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22 Note that this passage was published by some of the same authors who are central to my reports and who were later funded by Big Pharma. I refer to this publication as the “Earlier Report.” “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 2005


24 “No certain predictors for mutation status in a Danish cohort with familial hypercholesterolemia: A descriptive study” Mads Nybo, Klaus Brusgaard, Annebirt Bo Hansen; 2007
Part 2: The Patient Swap

The fact that mutations are milder is both a health benefit and a financial problem

There is a health benefit with Cascade Screening\textsuperscript{25} -- and a financial benefit too, albeit for insurance carriers and Medicaid, not for pharmaceutical companies. Cascade Screening is highly effective in locating genuine FH. That's a big problem for commercial medicine. The patient identification procedure with the greatest efficiency is an unmentioned obstacle. Identifying the genuine FH presents several threats to Pharma’s marketing interests.

1. First, those with mild mutations are the majority of carriers.
2. Their mildness undermines the marketing message of “urgency.”
3. They are milder, it is speculated, because environmental factors often do play a role in cholesterol levels. Thus, there are other remedies. Even when these milder mutations are found, doctors will be less likely to prescribe risky and expensive drugs.
4. Lastly, “Precision Medicine” is the future, leaving these Pharma profits vulnerable to increased public exposure to the fact that mutations are milder, threatening to expose all of the above and more: “Underdiagnosis” is not only proven, but given awareness of the problem, touting the scoring system as sufficient causes underdiagnosis.

When the medical solution is a financial problem, ethical conduct needs to step forward. Should the industry mitigate the risks of selling off-label? If the genuine carriers are milder than previously thought and if environmental factors do play a role, then there is an overlap of carriers and non-carriers, both above and below clinical passing scores. Setting aside Cascade Screening, if Pharma is truly concerned with “precision medicine” then they should use the two procedures, not as a choice between alternatives, but as two necessary steps in a procedure of elimination.

1) It is prohibitively expensive and structurally impossible to genetically test entire populations. So the first step is practical: scoring systems. But with this, the milder mutation carriers are eliminated from consideration – the majority of carriers.
2) Also, most of those with passing scores will not be FH carriers. So genetic testing is the second step. We want to eliminate the non-carriers, just as a detective uses forensic DNA matching to eliminate the innocent from his list of suspects. The non-mutation carriers are eliminated here – the majority of those who survived the 1st step.

“Commercial Medicine” is full of irony. For a CEO, the solution to the problem of finding the FH mutation carriers comes with the problem of finding them. They are milder than previously thought. Mitigating the risks of off-label sales through the diagnostic scoring systems, as always, presents a problem for profits. Drug sales are now a fraction of what they were. Pharma’s problem with genetic approaches to FH is not the severity of the disease, but the mildness – not medical, but financial. However, Pharma has found a financial solution to the problem of diagnostic accuracy: inaccuracy.

\textsuperscript{25} Cascade Screening is a strategy for genetic testing: it traces family lines and uses centralized databases to improve the odds of finding genetic matches. Cascade Screening has been used in the Netherlands with great success. Pharma’s publications do mention Cascade Screening, but they keep the more profitable scoring systems front and center. (The USA is not equipped for widespread Cascade screening. For example, “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. See page 86.)
Lowering identification standards increases the resulting population

The potential conflict between genetic testing and the scoring systems is parallel to that of the two types of evidence within legal judgments: the weaker forms of circumstantial evidence and the forensic DNA match. With the circumstantial, the fewer characteristics there are, the larger our pool of suspects ... but we also increase the number of innocent included. When it comes to weighting circumstantial evidence, the error-rate is scalable, every notch lower in the standard for evaluation (threshold) increases the number of innocent in our pool, disproportionately -- because the number of the actual guilty remains fixed. On the other hand, a forensic DNA match, when done correctly, is not scalable. It is 1 match for 1 criminal.

In medicine, the terminology is different but the epistemological conflict is the same. This linguistic unfamiliarity is what Pharma-funded FH reports are trying to exploit. They reduce the standards of the scalable, circumstantial, scoring systems, while discouraging the more forensic genetic testing. They instruct the medical community to regard the results of these lower standards as something more than suspects: these are said to be the actual FH patients, in need of expensive, risky, new medicines. But if we lower the standards for accuracy we do not end up putting more FH on these risky drugs; we disproportionately prescribe the drugs to false positives.

We might as well give the gold medal to the archer who can paint the largest bull's eye rather than to the one with the better aim. In FH research, we find a target-painting contest, not archery.

Here's the big, unexpected problem when it comes to FH. Genetics, like forensics, is strong and precise. It reduces errors, settling for fewer FH determinations. A clinical scoring system, like circumstantial evidence, is weak and error-prone. It inflates the count with errors. This is why the accuracy of genetics works against the industry’s aim on profits, while the inaccuracy of the scoring system works for it.

This brings us to an apparent dilemma. Because the disease is milder than previously thought, if genetics is emphasized, Pharma loses the marketing message of “severity.” On the other hand, because environmental factors are at play (contrary to Pharma’s main message), there is an overlap of Non-FH with FH, and so lowering the standard of the scoring system captures more people. But at the same time, it actually increases the decibels behind the bias of “Severity!” How does this work?

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26 Academically, it can be argued that ultimately all evidence is circumstantial. When I speak of “circumstantial” evidence, I mean the weaker forms of circumstantial evidence. When I use the term, “forensic,” I mean a decisive fact, such as finding a DNA match. For the current analysis, I intend a distinction between these two terms according to their base rate. For example, a characteristic associated with a bank robber -- a red baseball cap -- may be shared with other suspects. There are five people with red baseball caps in the vicinity. Thus, the odds of any given wearer of red baseball caps being the actual criminal is 1 out 5 suspects. These are very poor odds if sighting someone with a red baseball cap is my only criteria. I dismiss this single, isolated fact because it is “merely circumstantial.” On the contrary, if DNA evidence was left behind, and competently analyzed, we would say that the odds of a suspect with the same DNA being the actual criminal is 1 out of 1. That particular DNA is a characteristic unshared with all other suspects in the vicinity. So when I use the words, “circumstantial evidence,” I mean a weaker base rate which is relies upon characteristics shared with others, and when I say forensic, I mean the strongest base rate: 1 in 1. It relies on a characteristic unshared with all others.
The problem of mild mutations: Selection Bias and use of the scoring systems

The erroneous assumption and prevailing prejudice that most FH mutations would have severe consequences is partly due to the preservation of selection bias within Pharma-funded reports.

Here's an example: If I wanted to identify NBA players in the general population, I could look for individual characteristics of NBA players, such as an above average height. All those whose heights were above a “cutoff point,” which I myself would determine, would be defined as “NBA players.” If I then averaged the heights of all those on my list, the results would in all likelihood suffer from selection bias. This is because the stereotype that NBA players are taller than average results in a cutoff point which necessarily excludes any NBA players who do not exceed this cutoff point. Any shorter but genuine professional players cannot possibly be included in the tally. If there are players who are not as tall as my cutoff point, then by mathematical necessity, the average height of NBA players now appears to be higher than it actually is. This bias is due to my faulty selection procedure.

However, when I average all actual players on the NBA roster, I will have to include these shorter players – those who had been excluded by the cutoff point in the scoring system.

So if there are actually players with heights below my imposed threshold, the results from the official NBA roster will necessarily reveal a lower average height. And when the average height of all players on the roster is lower than that of those in the scoring system, it is the scoring system that is biased and incorrect.

- Any average determined by a cutoff point above the minimum will necessarily be greater than the average of the total.
Simple example: how switching identification procedures swaps patients

Here is a concrete example. We want to count gannets.

1. There is one gannet above the water.
2. There are two gannets under the water.
3. There are two pigeons above the water and pigeons don’t swim.
4. At any given time, the gannets under the water cannot be the gannets above the water.
5. And by genetic definition the gannets cannot be the pigeons.
6. Thus, we are confronted with two genetically defined species and two circumstances.

7. **Forensic Procedure**: If I select and define my population of “gannets” by way of DNA identification, I identify the one gannet which was above the water and the two gannets that were under the water. The pigeons are not a genetic match, and so I eliminate them from the count. What underlies my claim of “three gannets” are all gannets.

8. **Circumstantial Procedure**: Later, I select and define my population of “gannets” by the circumstance where gannets spend a lot of time -- *flying above the sea*. My conclusion is human but untenable, “Therefore, what flies above the sea is a gannet.” If I find three birds above the water, I simply check them off on my clipboard, calling them “three gannets” … because they fit the circumstantial definition imposed upon them by my chosen identification procedure. I have one gannet, it is true, but I also have two pigeons which are simply renamed, “gannets,” because they happened to be flying above the water too.

9. If I use the DNA examination (7) to *prove* to a purchaser how many gannets there are but then *use* the circumstantial definition (8) when actually *selling* them, I swap out the submerged gannets used in the advertisement and swap in the pigeons for the sale, employing a bait-and-switch scheme.

“Above” and “Below” the water is above and below a circumstantial cutoff point. Given that DNA testing put us closer to the original aim and established a statistical fact, opting later for a circumstantial judgment effectively de-identifies the underwater gannets and the flying pigeons, swapping them when switching identification procedures. The transfer is the same when the FH were first identified in genetic terms when claiming prevalence and underdiagnosis, but then later identified circumstantially when sold treatments.

**If we begin with the genetic procedure and then move to the circumstantial, selection bias de-identifies the target and de-identifies the off-target, swapping them.**

![Diagram of gannets and pigeons]
Euclidean Precision: A swap is undeniable and follows from a “poisoned premise”

The poisoned premise: what is claimed to be a defining characteristic actually has an equally pervasive variety in two populations. More specifically to our topic, scores based on defining characteristics have an equally pervasive variety in both a target and an off-target population. Of course, this is a contradiction: it’s not really “defining” if the characteristic is shared with an off-target population. With this premise, the argument has already swallowed a poison-pill and cannot be saved. The swap must follow by mathematical necessity. There are two critical points:

Point 1, Left: The two words, “defining characteristic,” is a misunderstanding in this context. We make distinctions with differences and cannot make them with similarities. Despite the connotation of “differences” in the usual usage of the word, “variety,” a similar variety in two populations is still a similarity and not a difference. This misunderstanding, unchallenged, effectively relabels the off-target as the target population: due to similarity of variety, the cutoff point involves no true distinguishing characteristic.

Point 2, Right: Any cutoff point at the absolute minimum is meaningless; it is synonymous with the entire population. Any cutoff point anywhere above the minimum necessarily excludes all below itself.

Below, review of the mathematical necessity of the swap:

- The threshold of any scoring system cannot make the intended distinction if the “defining characteristics” of its intended target are also similarly present in the off-target population. Imposing the cutoff point does not “identify” the target. It simply confuses the higher scores with the intended target. It inflates the results with errors.
- With an equally pervasive variety, a scoring system cannot overcome the existence of those below the cutoff point. Imposing the cutoff point not only fails to “identify” the target accurately; it actually abandons a portion of them.

If the “defining characteristic,” or scores based on characteristics, has an equally pervasive variety in both the target and the off-target, then the swap is undeniable and can be demonstrated with Euclidean precision.

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<tr>
<th>Scores of Target</th>
<th>Scores of Off-target</th>
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<tr>
<td>5</td>
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<td>4</td>
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Cutoff points are meaningless here.

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<th>Variability of Measurements</th>
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<tbody>
<tr>
<td>5</td>
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<tr>
<td>4</td>
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<tr>
<td>3</td>
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<td>2</td>
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<td>1</td>
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Selected cutoff point excludes all lower scores.
Likewise, the single, poisoned premise exists within the Regeneron Report

The Regeneron report claims, “A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network Criteria (DLCN).” This statement is contradicted by the report. Although distribution of the scores in the FH target and off-target populations is not precisely equal, the variability seen in the Regeneron report is enough to make the swap of the majority of mutation carriers undeniable. FH scoring systems, as if sufficient in and of themselves, do not work. The reports’ own published data proves the selection bias at work here.

The scores from the “DLCN” and other such scoring systems have a similar variability in both the FH sample and in the remaining population. This single premise of similarity where distinction is required is all that we need: the swap then follows by the immutable laws of mathematics. With a similar variability of FH scores pervading two populations, any cutoff point above any minimum score necessarily precludes all those below itself, while that similarity also precludes use of the cutoff point to make a distinction between all those above itself. With this poisoned premise, switching from genetic matching to cutoffs in a scoring system, the swap of patients is a mathematical necessity. (See the previous page.)

The scoring systems may help concentrate the pool of suspects, but the result is still grossly inflated with false positives. We may begin 1:250 ~ 1:500, and after scoring, end with 1:10, but we still inflate the results with 90% false positives. A genetic match on the other hand ends with a rate of 1:1.

Recommending such scoring systems as if sufficient to identify FH is more than just bad faith. A critical, mathematical fracture is at work: when entire populations are tested for FH, most mutation carriers do not pass the scoring systems and most who pass the scoring systems are not mutation carriers. Thus, there is a swap of people that takes place when we switch from a genetic identification procedure to a circumstantial scoring system.

In a marketing environment, when one such procedure is used for advertising and the other for the point of sale, swapping the item of purchase, we have a scheme that is called “bait-and-switch.”
The poisoned premise in the Danish reports

The 1st and 2nd Danish reports only tested for the 4 most frequent mutations. In the 2nd report, the authors used a ratio to calculate the remaining mutations. However, even when using the raw data, one can see the contours of the problem. (Right) The scores have a similar variability in both the target sample and in the total population. As we’ve seen in the previous two pages, this single premise of similarity where distinction is required is all that we need to prove the swap.

Accounting for the remaining mutations which were not screened for makes things a bit more complex, but doing so renders the swap conspicuous (along with other shenanigans). The 1st report used mostly a circumstantial scoring system for the results ("Phenotyping"). The 2nd report used genetic testing for its prevalence result ("Genotyping"). Now, industry-funded reports define FH genetically when assessing the urgency of underdiagnosis and then recommend the scoring procedure for actually finding patients for prescriptions.

Swap out: The recommended cutoff point as “Probable and Definite FH” excludes the majority of mutation carriers.

Swap In: With the recommended FH scoring system, as if sufficient, the higher scoring 4 most frequent carriers (right column) are indistinguishable from the higher scoring in the off-target population (left column of numbers).

➢ Therefore, the two Danish reports serve as a proxy for the industry’s publication strategy. When we reconcile the 2nd and 1st Danish reports we are also reconciling the two procedures promoted by the industry: one for prevalence (“underdiagnosis”) and the other for diagnosis (prescription sales).

How does this work out?

What at first appears to be mathematical “whack-a-mole” ends up as a static, well-defined swap of patients:

- It is mathematically impossible for the genetic-based results in the 2nd report to be correct and for the results of 1st report’s scoring system not to be inflated with false positives.
- Moving from genetic matching to circumstantial scoring, we identify different people.

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27 I.E., without considering the less frequent mutations which were not included in the study.
The reconciliation of the 1st and 2nd Danish report procedures, a summary

My original analysis of these two reports is decisive. I was assisted by the fact that FH is a genetic disease, and thus there is a mathematical and forensic rigor operating in the background of this problem. Additionally, both Danish reports shared the same core population, presenting opportunities for deduction.

The deductive reconciliation of the two reports was quite elaborate. The summary illustration below is a representation of the conclusion.

To emphasize this crucial point, the reconciliation of the two reports serves as a proxy for the industry’s publication strategy, as can be seen in the recent Regeneron report: when we reconcile the prevalence and diagnostic procedures found within the publication strategy, the force of deduction exposes the bait-and-switch: it is impossible for the same people to be both above and below clinical detection at the same time.

Charts of the Deductive Reconciliation of the 1st and 2nd Danish Reports

The 1st report did not break down genetic hits into their original scores: before publication, they were promoted to passing scores. Unraveling the original scores of these hits also unraveled the publication scheme. The authors’ resource for both publications was key to the solution: the 2nd Danish report used a population of roughly 100,000 people; but roughly 60,000 of these were the very same people used in the 1st Danish report. This shared population thus created an opportunity for deductive analysis. Taking the 2nd report’s number of genetic hits which were also passing clinical scores as the maximum mathematically possible in the corresponding category in the 1st report showed that patients are swapped as we move from the genetic-based to clinical scoring procedures. There were only 25 of the four most frequent mutations which had passing scores among the 2nd report’s 100,000; this meant that the portion of 60,000 used in the 1st report could not possibly have had more than 25 such carriers, just as it is impossible for the slice to be larger than the pie out of which it is cut. The higher the number of mutation
hits the fewer false positives there will be in the result. Thus, to give the authors the best footing mathematically possible, but also to eliminate any doubt whatsoever, I used the entire 25 on the 1st report as a “deductive ceiling” -- higher numbers are mathematically impossible. (Later in that report, I also estimated what this number might have actually been and arrived at 15.) In the chart below, we use the 1st report’s data, but on the left we employ the 2nd report’s procedure and on the right, the 1st report’s procedure.

Only the four most frequent mutations were targeted. In the chart below, I call these the “Top 4.” I call the remaining mutations the “Ex-Top 4.” The 2nd report uses 38.7% as the proportion of Top 4, thus enabling a calculation of the Ex-Top 4. (See the full report for a step-by-step demonstration: http://FHprevalence.com.)

Those counted genetically are different people from those counted with the scoring system. As a proxy for the industry’s publication strategy, we can see that the very people used to prove underdiagnosis in the determination of FH prevalence are abandoned and replaced with errors at the diagnostic stage. This 1st report was purported to be the “source” for the industry’s Authoritative report, the latter being cited even in FDA submitted documents.

What if we apply the 1st report’s method to the 2nd report’s data? These two procedures are two separate perspectives within the same population, and according to the authors, the results of the 2nd report were roughly “comparable” with those of the 1st report … which suggested a confirmation of the results. However, this is incorrect. Equal quantities still beg the question of the underlying entities. I may have two elephants over there and two mice over here, but their equal quantity does not change mice into elephants.

The “poisoned premise”: With a similar variability of FH scores pervading two populations, any cutoff point above any minimum score necessarily precludes all those below itself, while that similarity also precludes use of the cutoff point to make a distinction between all those above itself. With this poisoned premise, switching from genetic matching to cutoffs in a scoring system, the swap of patients is a mathematical necessity.
Using the 1st report’s method on the 2nd report’s data (right chart) would inflate the results with false positives, while swapping out genuine mutation carriers (left chart). 60% of those in the 1st report are also present here in the 2nd report. We cannot use the authors’ two prevalence rates above for comparison. They refer to mostly different people. The 1st report, the one inflated with false positives, 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.

As mentioned, the 2nd report uses 38.7% as the proportion of Top 4 to total carriers. From there the authors calculate the total, which is supposed to account for the number of those with the mutations that were not targeted in the study. The 1st report, on the other hand, simply leaves it to the reader to assume, as is only natural, that the scoring results minus the four most frequent mutations (the “Top 4”) must equal the remaining carriers. They do not. This is key to the error in the 1st report, and this error can be captured in mathematical equations: see the following page for the mathematical proof, page 59.
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:** The 2nd report shows us that identification of one portion of mutation carriers was not *physically* possible within the 1st report’s methodology. Thus, their exclusion from the 1st report’s *Total*, while nonetheless calculated *within the naturally assumed 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 + \( \frac{AT+BT}{R} \) – 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

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<th>T</th>
<th>X</th>
<th>FP</th>
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<tr>
<td>A</td>
<td>≤25</td>
<td>≤40</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>≥75</td>
<td>≥119</td>
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**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, BT cannot possibly be less than 75 in the 1st report.

AX = AT/.387 – AT

≤25/.387 – ≤25 = AX

AX ≤ 40

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.

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

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<tr>
<th></th>
<th>T</th>
<th>X</th>
<th>FP</th>
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<tr>
<td>A+B</td>
<td>100</td>
<td>159</td>
<td>144</td>
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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 possible patients, while the most profitable false positives only require the acceptance of this procedure. The unmentioned gap in the math allows a clinical procedure which effectively renames these errors as “FH,” 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.”
**Reversing** the procedural steps increases the risks of off-label sales

The same steps in a different sequence result in very different populations. The first step, as any good detective knows, is to create a list of suspects, and which may include the weaker forms of circumstantial evidence. We start with a wide net. The second step is to eliminate suspects from the pool through more decisive evidence. The FH industry *reverses* this more accurate epistemological sequence, and uses genetic testing only to sound the alarm, and then as the final step, *recommends* the circumstantial scoring systems. *Most mutations are actually milder than previously thought and these milder mutations will remain undetected.* At the same time, the scoring systems swap in Non-FH. **Switching procedures for the point of sale is more profitable for Big Pharma.**

![Diagram of procedural steps]

(Note that both sequences abandon the milder FH. The solution lies with the industry’s third option, “Cascade Screening.” But with that, profitability would be reduced. See page 49.)

Genetic matching has value as an advertisement and as a legal and professional disclaimer, not as the procedure used at the point-of-sale -- *diagnosis for prescriptions.* Thus, the *procedural steps which mitigate risks are reversed.*

On the following page, I provide additional proof of this reversal. I have pasted a few screenshots along with my comments and analysis: the upper illustration concerns the 2nd Danish report, and the lower illustration, the Regeneron report. (For the chapter that will follow, note how the reports declare genetic testing to be uncommon and unavailable.)

**2nd Step 1st Step:** Genetic testing is only performed to claim “underdiagnosis” academically. It thus includes the milder mutation carriers. *It is not practical however to test entire populations genetically.*
**Regeneron Report**

A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network (DLCN), Simon Broome, or Make Early Diagnosis to Prevent Early Death (MEDPED). These diagnostic tools estimate the likelihood of FH on the basis of clinical features and, in the case of DLCN and Simon Broome criteria, also include identification of functional variants in the LDLR, APOB, or PCSK9 genes. However, genetic testing for these variants is uncommon in clinical practice in the United States.

**2nd Danish Report**

Bait: First, step 1(a) linguistically conflates different diseases (above) and (b) uses genetic identification as the counting procedure for prevalence, advertising the emergency of “underdiagnosis”...

Genetic-based prevalence proves underdiagnosis.

Excluded in step 1 but included in step 2.

Net result of the sequence of steps 1 and 2 is a swap.

Included in step 1 then excluded in step 2.

**Passing Scores & Genetic Hits**

Passing Scores with no Genetic Hits

Recommended scoring system, mostly Non-FH.

**Switch:** ... then step 2 uses scoring systems with cutoff points for diagnosis, switching identification procedures at the point of sale. This excludes most of the difficult-to-find mutation carriers, and in their stead, this circumstantial approach includes mostly non-carriers, which are effectively re-named, “FH.”

Known FH-causing mutations are expected to occur in 1/217 in the general population in Copenhagen and are best identified by a definite or probable phenotypic diagnosis of FH based on the DLCN criteria, or an LDL cholesterol above 4.4 mmol/L and particularly in individuals below 40 years of age. Genetic screening facilitates diagnosis and risk assessment of FH; however, 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.

**Switch:** ... then step 2 uses scoring systems with cutoff points for diagnosis, switching identification procedures at the point of sale. This excludes most of the difficult-to-find mutation carriers, and in their stead, this circumstantial approach includes mostly non-carriers, which are effectively re-named, “FH.”

Net: the 2nd report did not actually screen for PCSK9. Nonetheless, it contributes to the cultural misunderstanding. PCSK9, “FHS,” is now “FH.”

2nd Report, concluding paragraph

Disregard the fact that this is a disease defined by a genetic mutation.

**Regeneron Report**

“FDB” becomes “FH”

“FH3” becomes “FH”

Associated with cardiovascular mortality and morbidity: Pathogenic variants in three genes (LDLR, APOB, and PCSK9) account for the majority of FH cases. We assessed the prevalence and clinical impact of FH-associated genetic variants.

Genetic-based prevalence proves underdiagnosis.

Excluded in step 1 but included in step 2.

Net result of the sequence of steps 1 and 2 is a swap.

Included in step 1 then excluded in step 2.

**Passing Scores with Genetic basis**

Passing Scores with no Genetic basis

Recommended scoring system, mostly Non-FH.

2nd Report

“FH”

“FDB” becomes “FH”

Note: the 2nd report did not actually screen for PCSK9. Nonetheless, it contributes to the cultural misunderstanding. PCSK9, “FHS,” is now “FH.”

Regeneron Report

“A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network (DLCN), Simon Broome, or Make Early Diagnosis to Prevent Early Death (MEDPED). These diagnostic tools estimate the likelihood of FH on the basis of clinical features and, in the case of DLCN and Simon Broome criteria, also include identification of functional variants in the LDLR, APOB, or PCSK9 genes. However, genetic testing for these variants is uncommon in clinical practice in the United States.”

Therefore, the default procedure is step 2, the scoring systems.
To conclude with a recommendation to disregard the presence of a mutation, after having just stressed the urgency of a disease defined by the presence of a mutation, makes no sense. Dismissing genotyping (genetic testing) while recommending phenotyping (circumstantial characteristics) recommends the swapping out of genuine patients to swap in their look-alikes, their stereotypes.
Industry and author awareness of selection bias and milder mutations

A selection bias in FH scoring systems was the very conclusion made by three of the authors of the Danish reports, in their Earlier report: scoring systems exaggerate LDL levels to the upside. It then follows then: the FH mutations were also milder than previously thought. This is only possible if there is a variability of scores present in the FH. The excerpts below say as much. No one disputes that this variability is also present among the non-FH. And as we have seen, because the variability is present in both populations, there is a “poisoned premise” within FH scoring systems, after which the industry’s recommended diagnostic procedure fails and the swap of patients becomes a mathematical necessity.

2005: “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 DOI: 10.1161/01.ATV.0000149380.94984.f0

They write:

“The effect of mutations on phenotype is often overestimated because of ascertainment bias.”

“Ascertainment bias” is an academic term for the selection bias that concerns the authors. Their conclusion is not possible without two elements of selection bias: first, all those who have been selected for referrals to a clinic tend to have more severe symptoms than those carriers who did not receive referrals, and second, those genuine carriers who do not have passing clinical scores had been precluded from the tally in previous studies. In short, a group of mutation carriers found by testing a randomly selected population of 10,000 (thus, “unselected”) is compared to a group selected by the “Simon Broome criteria,” the latter being one of the FH scoring systems.

Here is a comparison of the selected population against the unselected one:

“Furthermore, background population was a significant determinant of the apparent phenotype associated with these mutations: carriers identified among patients with IHD or clinical FH had increasingly higher levels of cholesterol compared with carriers in the general population.”

Here is a threat to Big Pharma profits: evidence that environmental factors play a role in LDL levels. This takes away from the industry’s argument that expensive medications are the only solution for mutation carriers.

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28 For an explanation of selection bias, see page 51.
29 For an explanation of the “poisoned premise,” see page 53.
“Effect of Background Population on Phenotype: Importance of Ascertainment Bias

Heterozygous carriers of LDLR mutations with IHD or FH had cholesterol levels that were on average 1.2 and 2.0 mmol/L higher than in carriers identified in the general population. 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.”

And ...

“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: age, gender, and body mass index.”

And here is another statement on the effects of selection bias on FH studies.

“In further support of our conclusion that cholesterol levels associated with a given mutation are overestimated among patients with IHD or FH is the fact that we found the exact same results for APOB R3500Q when identified in similar background populations. Finally, that phenotype associated with a given mutation is overestimated in patients has also clearly been demonstrated by us and others for hemochromatosis mutations, and for factor V Leiden and venous thrombosis.”

The final sentence:

“In conclusion, our results suggest that the phenotype associated with a given mutation should not be determined in patients, but rather in unselected individuals in the general population.”

Other authors prove the cultural awareness of the variability of the characteristics (phenotype) of FH

“FH is a disease that shows great phenotypic variability.”... “A study on 643 Danish probands could not even find a single phenotypic characteristic to predict the existence of a mutation.”

“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.”

“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.”

30 Familial Hypercholesterolemia: The Lipids or the Genes? Akl C Fahed and Georges M Nemer; 2011
31 Mechanisms of Disease: genetic causes of familial hypercholesterolemia; Anne K Soutar and Rossi P Naoumova 2007
32 No certain predictors for mutation status in a Danish cohort with familial hypercholesterolemia: A descriptive study Mads Nybo, Klaus Brusgaard, Annebirthe Bo Hansen; 2007
Key authors first show awareness of selection bias then reverse themselves later

2005: **Anne Tybjærg-Hansen, Marianne Benn, Børge G. Nordestgaard** (and others) write their Earlier 2005 report on the selection bias inherent in FH clinical scoring systems. This shows that these three were aware when they later reverse and employ that bias in 2012.

2012: **Anne Tybjærg-Hansen, Marianne Benn, and Børge G. Nordestgaard** co-author this 1st report and the later 2nd report. *They reverse themselves.* Three of the 2005 authors completely ignored their own previous exposure of the selection bias and then used it in this 2012 report. (**Gerald F. Watts** will join them here.) Watts and Nordestgaard disclose heavy funding from various Pharmaceutical companies, including but not limited to Amgen and Sanofi-Aventis.

2013: Three of the above 2012 authors show up again. **Nordestgaard** will be the lead author to the industry’s Authoritative report, the 2013 EAS “consensus” report, which claims the 2012 1st Danish report as its source. **Tybjærg-Hansen** and **Watts** will be co-authors, among others. Again, they recommend the scoring systems. There is heavy Pharma funding.

2016: **Anne Tybjærg-Hansen, Marianne Benn, Gerald F. Watts** and **Børge G. Nordestgaard** co-author the 2nd Danish report – stating results “comparable” to the 2012 1st Danish report. But this recent 2016 report actually provides the detail with which we can make decisive deductions, refuting their own former 2012 research. The authors again recommend the scoring systems.
Who is the European Atherosclerosis Society? What do they do?
The 2013 and 2014 EAS reports had large pharma footprints. Amgen, Aegerion, etc. The data had already been roughed up in the 2012 Danish and 2014 Dutch reports. Through citation kiting the confusion is compounded and it takes some historical digging in order to recognize that the threads between publications aren’t really tied together. Once the work is put in, however, the issue is not fuzzy or questionable. There is a clear, bright line with undeniable boundaries: a claim of a reality is set to a historical record and it is contradicted by that very reality – a subsequent chapter in that historical record.

When journals collaborate with goals common to commercial enterprises, how are they different from serving as de facto marketing divisions? Having “common goals” and “mutual strategies” with “corporate partners” is a collaboration between financially interested parties, not a collaboration whose definition of “scientific” depends upon real independence. EAS sounds and behaves like a publication-strategy organization. Also, these are not insulated ... independent publications whose teams are unaffiliated with one another. These are repeat-authors, with repeat-funders.
As I have demonstrated, the EAS material is distorted through the simple mechanism of citation kiting. This involves coordination among authors shared across publications and organizations: there are authors on both the Dutch and Danish reports, the “sources,” who are needles that run through and stitch both sets of publications -- the source material and the EAS consensus papers -- with the wrong names and numbers. Facts are switched from paper to paper, not passed on. On the right are the two “relay teams” that “switch the baton” instead of passing it on fairly.
Publication strategy services and “relay teams”

Many members of the 2013 and 2014 EAS consensus panels of experts have apparently followed on with Translational Medicine Academy (TMA), a group which, among other questionable services, advertises help with publication strategy formation and development of Key Opinion Leaders. Many of these EAS “panel experts” appear to be scientists for hire. Amgen is a TMA partner. (See page 71.) TMA advertises that they will help such organizations form consensus reports. On the TMA website John Chapman is advertised, and his bio lists him as EAS president during the time period of the 2013 and 2014 consensus reports. In fact, according to the bio he “spearheaded the EAS Consensus Panel initiatives,” and “these publications achieved wide visibility.” Indeed, according to the EAS reports themselves he was organizer, along with Dr. Ginsberg. Archive.org shows him as president of EAS in 2012. So, here he is with TMA. What service is being advertised? What is Dr. John Chapman’s role here? Is it different from his role in EAS? Right: Services TMA advertises include, “Expert Symposia” … “Expert Statements/Position Papers.” And that’s what Dr. Chapman did for EAS. This suggests a marketing service insulated by the prestige and assumed legal protection that comes with recruiting and presenting Key Opinion leaders … peers and experts.

Are independent scientists a problem? TMA advertises its marketing services as a solution to a problem which is in large part inherent in the independence of scientists: “Traditionally, medical research has been compartmentalized.” A scientist seeking an independent conclusion will “compartmentalize” his efforts and analyses … seeking separation from other scientists and especially from prevailing dogma. That’s science. Bringing everyone together to get a product to the market is a commercial effort, even if that product ultimately benefits patients. TMA will be the ones to bring it all together, “Free of the red tape and hierarchies that can hamper agencies and international organizations, TMA is well positioned to bring together stakeholders to work towards filling knowledge gaps and overcoming hurdles to improved clinical care.” This puts organizations like TMA in the central role … a sort of master key for all the different doors to the different departments within a given drug-venture. But this is also tantamount to taking responsibility for the integrity of the information its paid team members “bring together” for the rest of us.
“TMA develops these programs with key opinion leaders working in specific medical fields and with experts in medical practice and research, with a view to finding solutions within the translational medicine paradigm and deliver them to patients.”

Translating medical technology into sales is called “commercialization.” But translating a discovered medical treatment into clinical practice involves sales to patients. It’s called, “Translational Medicine.” Call each what you will, whichever one you shine a light on, the other is the shadow you will see. Now, many of the EAS “relay team” are here with TMA:

### Members of the EAS relay team who are with TMA

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<td><strong>Gerald F. Watts</strong></td>
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(*Ghost writer? Not listed under the title as an author, but the email j.s.jansen@amc.uva.nl is listed at the bottom of the page as “Corresponding author.” The European Cooperation in Science and Technology (“COST”) lists Erik Stroes with this email as contact.)

I’ll step back here. TMA is so over-the-top that I do question whether or not some claims are real. Why is the TMA U.S. address listed online as a nail salon?

How much of TMA is real? However, if the website does represent Dr. Chapman’s and others’ participation accurately, it suggests a willingness of these EAS authors to profit from corporate needs by trading in their scientific reputations.

Is it only a quibble to comment on the phrase, “The TMA uses Evidence Building, Education, and Advocacy Programs to address these needs”…? First, a scientist does not build evidence, but finds it. Second, will we be educating doctors or misleading them if we recruit personnel with histories of citation kiting? And whose interests are really advocated in an “advocacy program” which is touted in a solicitation for corporate funding?
According to TMA, Amgen is a “Partner.”

On the left, within the FDA, Amgen uses the EAS report to claim the increased prevalence estimate. On the right, Amgen is a partner with TMA. The two organizations, EAS and TMA, ally their publication efforts with Pharma’s commercial goals. Citation kiting in the 2013 and 2014 EAS reports is indisputable, and the consequences are hazardous. Many of the same authors on the EAS report are advertised on TMA’s website. This illustrates in broad strokes an unhealthy alliance between commercial Pharma and Academia.

Here are more gems from TMA:

“Key Opinion Leader Development: ... Developing a dissemination plan to cascade messages through the influence pyramid” ~ http://www.tmacademy.org/mission-areas/

“We are looking for authors in translational medicine. Interested in contributing? Do not hesitate to contact us or to send us any article that you would like to disseminate worldwide. info@tmacademy.org”
**Last note on these authors and Pharma partners:** These conflicts of interest are not limited to the EAS or TMA. Looking for a publication strategist? Let’s not forget the individual participant, Jane Stock — a for-hire Medical Writing Consultant who worked on many EAS projects, including the 2013 and 2014 EAS reports. On linkedin.com her job description reads, “**All aspects of writing; working with KOLs on peer-review manuscripts and advisory and boards, and strategic publication planning are specialties.**” This advertisement is for services greater than just technical writing.
Conclusion: The Evidence is Decisive

- A man is identified on video robbing a bank.
- Madoff’s trading strategy required more volume than existed in the entire options exchange.

In the above, the two types of thefts have different triggers for opening an investigation ... two types of initial evidence: one begins with video while the other begins with analysis. Both of these pieces of evidence are strong, even though the former can be readily understood by the casual observer, while the latter requires some mental effort and deductive ability. Yet setting aside the difference of epistemological category, both are nonetheless very strong. Unfortunately, the crimes that harm the most people often yield the least concrete evidence. There was no gotcha-video for Madoff’s crime. No fingerprints. Nonetheless, the evidence against Madoff was not “fuzzy” or “circumstantial.” It could be tested in the real world for forensic evidence: trading identification numbers should be held by Madoff and these should be matched with actual trading at the exchange. Such a forensic reconciliation would be decisive. But that does not mean that the deductive analysis which prompted the search for forensic evidence was any less certain.

Likewise, the analysis I present is not “fuzzy logic.” This is not a “gray area.” It is not circumstantial. This is a mathematical fracture which can be demonstrated with Euclidean precision. The real-world consequences of switching the identification procedures can be demonstrated in mathematical equations, and this clearly shows the swapping of the FH for the non-FH patients. It can be tested in the real world for forensic evidence: My forensic reconciliation of the two Danish reports is decisive. The real people found through the 1st report’s scoring system can be reconciled with the real people found through the 2nd report’s genetic matching: they are not the same people. These two Danish reports serve as a proxy for the industry’s publication strategy: use the forensic, genetic approach to advertise the urgency of underdiagnosis, but then switch to a circumstantial system to locate mostly different people for the sale of Pharma’s drugs.

I am naïve and so I believe that because there is deceit and injury, some US law must have been broken ... but then what law? I look for other examples of this scheme as a form of human trafficking, but I find no prosecution as such.

1. Where Real people are recruited ...
2. By means of deceit ...
3. For the commercial exploitation of their bodies and the commercial manipulation of their organs ...
4. And the injury not done for medical reasons, but for profit, being violence, not medicine ...
5. What crime is that?

I do however know this. A clear forensically available line has been crossed. If the majority of genetic hits are below clinical detection and the majority above clinical detection are not mutation carriers, then what happens when we move from the genetic-based proof of “underdiagnosis” to the recommended clinical-based diagnosis? Underdiagnosis again ... but this time, an intentional, profitable one. Underdiagnosis does not just continue; it is caused. It’s not a medical problem, but a part of a solution to a financial problem. The recommended diagnostic system abandons the very people used to claim “underdiagnosis” ... by targeting non-LDLR carriers.

Sales are to the wrong patients.

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33 Page 59.
Taxpayers, insurers, and the insured pay for it all. And in the end, this scheme can only fall apart as “precision medicine” moves forward. With this tremendous waste of time and resources, one wonders what good might have been accomplished in its stead?
Summary of the Linguistic Gimmick

How can one increase a prevalence rate without having to find more people? Linguistics. If zebras were suddenly called “horses,” would we have more of either or both in the world? Industry-funded reports on FH are more aptly called linguistic strategies than prevalence studies. Their claim of a higher than expected prevalence is necessary to sound the alarm of “underdiagnosis.”

I’ve taken screenshots from two FH reports and put them together in the presentation below. They illustrate the definitions before and after the change. On the left is a report from 2003, and on the right, Regeneron’s report from 2016. In 2003, FH referred to the presence of an LDLR mutation; FDB was different and referred to an APOB mutation, and FH3 was yet another disease name, and referred to PCSK9. These diseases were all under the umbrella acronym, “ADH” – which spells out to “Autosomal Dominant Hypercholesterolemia.” Now Big Pharma has funded reports which drop the umbrella, “ADH,” and take the subset of ADH named “FH” and make it the umbrella term for the other two diseases. FH is no longer alongside FDB and FH3, but the terms to distinguish FDB and FH3 are dropped, and their respective mutations, APOB and PCSK9, are no longer referred to as subsets to “ADH,” but to “FH.” It is as if the peas under the shells labeled “FDB” and “FH3” have been palmed and are next found under the FH “shell,” which now houses all ... the LDLR, the APOB and the PCSK9. FH becomes the main set ... the entire set, and conflated with the other two diseases.

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. But it is a commercial argument not a move toward the medical discipline which requires that we move toward clarity and detail, and not away from them. A deliberate move away from clarity and toward the obscure is not science, but obscurantism.

The math is basic, after the restoration of linguistic integrity. 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 and converting others to a new cultural usage. 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.
Analogy of Bait-and-Switch: 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.

Warden’s Publication strategy

- Fewer than expected
- Forensic testing is not yet common, and so ironically, circumstantial evidence, regarded as sufficient, contributes to the deficit of real criminal arrests.
- Minority among those with circumstantial evidence and also a minority among forensic matches.

Minority to each: Both circumstantial and forensic.

- Majority: Circumstantial but no forensic.
- Majority: Forensic but no circumstantial.

Forensic report scares with the truth that “criminals are getting away with it,” mildly offers a disclaimer of the “limitations to circumstantial evidence,” while presenting circumstantial evidence as standard practice = Swap.

There are more suspects that fit the circumstantial evidence than there are actual criminals. Most are innocent. But they are easy and cheap to find, the most profitable group. Without a forensic step, they are all defined as “criminals.”

The move from the forensic message to the cultural use of circumstantial evidence, swaps the innocent and the guilty.

Unexpectedly, the excess of fugitives begins here. Without forensic evidence, circumstantial evidence alone abandons this majority of criminals. But it is impractical to screen the entire population to find them. These are the least profitable for the warden.
Actuality of Bait-and-Switch: Big Pha’rma 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 aids 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.
Supplementary Material:

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<th>Date</th>
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<td>2012:</td>
<td>1st Report</td>
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<td>2013:</td>
<td>Influential, Authoritative Report</td>
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<td></td>
<td>Regeneron report</td>
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<td>Cascade Screening in the USA is not practiced</td>
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Page 78
The FH Foundation

The FH Foundation echoes the call for using the scoring systems. While not failing to mention genetic testing, the infrastructure for genetic testing is not there, and so the scoring systems remain a cultural *fait accompli*. The charity informs us, “FH is commonly diagnosed based on clinical criteria; however, there is genetic testing available.”

“However”...? The selection bias is put front and center and suggested as if it were sufficient. It is not. Genetic testing is here presented as an afterthought ... as if something peripheral. Instead of two steps to a single procedure, these are presented as independent, equally sufficient identification procedures.

The industry goes a step further and applies the scoring systems to large medical databases ... using an “Algorithm.”

But as an epistemological category, an “algorithm” for data-mining characteristics is synonymous with a “scoring system” based on characteristics. The “algorithms” proposed are based on circumstantial evidence. And as we saw in the preceding chapters, the swap is inherent in the math resulting from using circumstantial evidence where forensics is required: the pervasive variability of FH characteristics is the “poisoned premise” within any argument for an “algorithm” which is based on characteristics shared with other diseases. This is because there is no definitive characteristic for FH ... no “phenotype.”

“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.”

We saw the proof of this “poisoned premise” on page 53. The lack of a definitive phenotype for FH is fatal to any merely circumstantial scoring system. It is a truism: lacking a definable FH phenotype one cannot use phenotyping to identify FH. One cannot alter this epistemological type by changing its name from “DLCN” to “Algorithm.” It is still **circumstantial**. An “algorithm” in this case is just the same scoring system but with greater

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35 The FH Foundation is promoting an algorithm to find FH. This is the circumstantial approach on a computerized, national scale: [https://thefhfoundation.org/find-fh](https://thefhfoundation.org/find-fh)

36 “No certain predictors for mutation status in a Danish cohort with familial hypercholesterolemia: A descriptive study” Mads Nybo, Klaus Brusgaard, Annebirtie Bo Hansen; 2007
reach ... and advertised to doctors ... by a Pharma-funded “charity.”

The FH Foundation, a charity heavily funded by Pharma, claims: “While every detail of our lifestyle is important – the food we eat, our physical activity, whether we smoke or not – FH always requires medical treatment in addition to that.”

It is not true that FH “always” requires medical treatment, but it is true that saying such will solicit more sales for Big Pharma.

And in the Frequently Asked Questions:

(https://thefhfoundation.org)

https://thefhfoundation.org/about-fh/faq

9. I have been diagnosed with FH but I don’t want to take medication. Can I lower my cholesterol through a low-fat diet?

FH causes excessively high LDL-cholesterol levels. This is dangerous as it leads to cholesterol getting built up in your blood vessels, leading to atherosclerosis, heart attacks, and even death. While it is important to be mindful of your diet, this is almost never enough to manage your condition.

In all cases FH requires aggressive treatment. Consult an FH specialist to find the best therapy regime for you.

Actually, most FH mutations are milder than previously thought.37

The presentations are unbalanced: mutations are actually mild. This critical fact should have been highlighted, not thrown into the corner of the reports without further discussion.

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37 See pages 48 and 64.
2012: 1st Report
Marianne Benn, Gerald F. Watts, Anne Tybjaerg-Hansen, and Børge G. Nordestgaard

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)

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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, 16 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, >5 points) was 1:1000 (Figure 2). Interestingly, prevalence for definit-

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 pathogenic and 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).

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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Familial hypercholesterolemia causing mutations are estimated to occur in 1:217 in the general population and are best identified by a definite or probable phenotypic diagnosis of FH based on the DLDN criteria or an LDL-cholesterol above 4.4 mmol/L.

The best phenotypic predictors of an FH mutation were a definite and probable diagnosis of FH by the DLDN criteria, and an LDL cholesterol concentration above 4.4 mmol/L, particularly in individuals aged 22 years.

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A diagnosis of FH can be made with a validated set of criteria, such as those established by the Dutch Lipid Clinic Network (DLCN), Simon Broome, or Make Early Diagnosis to Prevent Early Death (MEDPED) ([1–7]). These diagnostic tools estimate the likelihood of FH on the basis of clinical features and, in the case of DLCN and Simon Broome criteria, also include identification of functional variants in the LDLR, APOB, or PCSK9 genes. However, genetic testing for these variants is uncommon in clinical practice in the United States. We thus sought to understand the prevalence and clinical impact of FH variants in a clinical cohort by analyzing genomic sequence and electronic health record (EHR) data from 50,725 individuals from the Geisinger Health System, an integrated health care system with provider services in Pennsylvania and New Jersey.
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