How Citation Kiting uses FH to misdiagnose FCH, METS, T2DM and the Obese

An evidentiary exhibit that supports my prior reports. See fhprevalence.com.

Without a knowledge of my earlier reports, the following analysis and evidence may not be immediately clear. In my prior reports, I showed how FH patients are swapped. Pharma-funded, peer reviewed medical reports have manipulated the established scientific record through an equivocation strategy which is carried forward through citation kiting. By altering the instructions for the identification of FH, new instructions swap out most of the genuine FH mutation carriers, who are difficult and expensive to find. What I present in this report is more evidence of that swap, but also, I present evidence of who is swapped in: the FCH.

Main Takeaway: There is evidence that the sufferers of the disease, familial combined hyperlipidemia (FCH) are the true targets when manipulating instructions for identifying the disease, familial hypercholesterolemia (FH). This is a financial scheme and not a scientific endeavor. The “medical reports” function as marketing brochures, redirecting doctors toward the misdiagnosis of the FCH.
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### Acronyms

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<th>Definition</th>
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<td>ADH</td>
<td>Autosomal dominant hypercholesterolemia, category heading to FH, FDB, and FH3</td>
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<td>FCH</td>
<td>Familial combined hyperlipidemia</td>
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<td>FDB</td>
<td>Familial defective apoB-100, defined by the presence of the APOB mutation</td>
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<td>FH</td>
<td>Familial hypercholesterolemia, defined by the presence of the LDLR mutation</td>
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<tr>
<td>FH3</td>
<td>Autosomal dominant FH3, defined by a PCSK9 defective gene</td>
</tr>
<tr>
<td>He</td>
<td>Heterozygous (E.G. HeFH = heterozygous familial hypercholesterolemia)</td>
</tr>
<tr>
<td>Ho</td>
<td>Homozygous (E.G. HoAD = homozygous autosomal dominant hypercholesterolemia)</td>
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<td>JCL</td>
<td>Journal of Clinical Lipidology</td>
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<td>METS</td>
<td>Metabolic syndrome</td>
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<td>Non-FH</td>
<td>High cholesterol, but the cause is acquired and not inherited</td>
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<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<td>TG</td>
<td>Triglyceride</td>
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### Outline

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<th>Already Established Literature</th>
<th>Fact-ectomy</th>
<th>Equivocation</th>
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<td>Prioritize Genetic Testing</td>
<td>Demote genetic testing, while promoting scoring systems which are based on circumstantial evidence: focus on characteristics of FH which are shared with other diseases.</td>
<td>The number of those misdiagnosed as FH increases as we lower standards for accuracy.</td>
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At the outset, the probability of any random person having FH is still 1/500. (If we say 1/200, we don’t change the point here.) FCH is much more frequent, 1/100. The original MEDPED base rate fallacy inherent in diagnostic scoring systems (which are really just a method of weighting what in a legal context is deemed a weaker form of circumstantial evidence). To leverage the “base rate,” or to put it differently, to increase the “prior probability,” the original MEDPED began with a verified mutation carrier. The chance of a 1st degree relative having a mutation is 50%. This 1st degree relative, other information lacking, will still have the 1/100 chance of having FCH. Thus, if we begin with the 1st degree relative of a verified FH carrier, we begin with a superior prior probability. The genius behind Roger Williams’ overcoming of base rate fallacy is that even if we don’t test the first degree relative for FH genetically, we can now lower the cholesterol threshold, and even eliminate some typical exclusionary criteria, and we still have a superior chance of identifying the FH.

The problem for Pharma is that the Netherlands applied Williams’ method in the world’s most exhaustive search for FH patients, to great success. This is a problem because FH mutations were found to be more variable and milder than previously thought. Fact-ectomies:

1. Remove mention of beginning with a verified mutation carrier and/or extensive research of family pedigrees.
2. Substitute for either of the above, a single relative with a history of heart problems – an isolated characteristic shared with both FCH and other causes of high cholesterol.

With this simple elimination from the scientific record, the default instruction now re-employs the very base rate fallacy that MEDPED had already overcome. Because the solutions to cognitive biases are, by definition, counterintuitive, any proponent of a balanced debate must now swim upstream the cultural inertia of this now highly distributed and promoted human bias.

Base rate fallacy is counterintuitive. (1) If this point is not immediately clear, please see Daniel Kahneman and Amos Tversky’s treatment of base rate fallacy: the section “Representativeness” within “Judgement under Uncertainty: Heuristics and Biases,” Science Vol. 185, Sept. 27, 1974. (Kahneman won the Nobel Prize for his collaborative work with Tversky. Unfortunately, Tversky died before the award was determined.) (2) We will cover Roger Williams’ and his original MEDPED system in later pages. Base rate fallacy is key to understanding the superiority of Williams’ system and the critical difference between beginning with a verified mutation carrier and the scoring systems today which actually discourage genetic testing and Williams’ original system. (Williams died tragically in Swiss Air 111, and his work has since been de-emphasized, and sometimes misrepresented.)

Barring genetic testing, exclude those with high Triglyceride (TG) -- otherwise you may accidently misdiagnose the familial combined hyperlipidemia (FCH), metabolic syndrome (METS), type 2 diabetes mellitus (T2DM), and the obese as FH.

Remove mention of TG as exclusionary criteria. Remove the warning about the scoring systems’ vulnerability to misdiagnosing the FCH as FH. Cholesterol is the dominating characteristic in the diagnostic scoring system for FH, but it is a characteristic shared with FCH, METS, T2DM and the obese. What separates FH from the others is its typically normal TG levels. Thus, if one removes concern for TG, one captures the off-target and calls them “FH.” 1

The resulting “FH” pool are both FCH and FH. As a bonus, METS, T2DM, and the Obese are also confused with FH.

However, because of the successful equivocation of the diagnostic procedure, the statistics resulting from studies employing the scoring systems will reveal “bulges” corresponding with the key distinguishing characteristics of the off-target diseases.
Peer reviewed reports at the center of my research

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<td>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</td>
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<td>2011: Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes; D. Meeike Kusters, Roeland Huijgen; Joep C. Defesche; Maud N. Vissers, Iris Kindt, Barbara A. Hutten and John J.P. Kastelein; Downloaded from UvA-DARE, the institutional repository of the University of Amsterdam (UvA) <a href="http://hdl.handle.net/11245/2.114966">http://hdl.handle.net/11245/2.114966</a></td>
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<td>2014: The doctor’s dilemma: Challenges in the diagnosis and care of homozygous familial hypercholesterolemia: Seth J. Baum, MD; <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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The rise and fall of precision medicine:

Goldstein, et al. 70’s and 80’s
Find and make clear distinctions between FH and FCH. TG levels are the distinguishing characteristic. Examination of family pedigrees is a crucial element to the genetic determination.

Williams, et al. 90’s
Show base rate superiority by beginning with 1st degree relatives of confirmed FH mutation carriers. Put out a specific warning about an FCH/FH overlap, and show how to exclude the FCH.

CASCADE programs 90’s
National Dutch screening program inspired by Williams' genealogical strategy: “Cascade screening.” Both economical and highly accurate. FH is milder than previously thought.

Goldberg, et al. 2011
Change what the acronym “FH” stands for, from familial hypercholesterolemia to familial hypercholesterolemias. The FDB and FH3 are now called, “FH.” De-emphasize the potential to misdiagnose the FCH, and also de-emphasize FCH’s distinguishing feature, higher TG. This neglect brings in FCH as “FH.”

Goldberg in Merck Manual 2018
Citation kiting has now cornered the Merck Manual. The only way for FH to refer solely to the LDLR mutation and have a prevalence of 1/200 is for the FDB (APOB carriers) to be double counted.

EAS expert consensus, 2014
Through citation kiting, a Dutch study is manipulated. Additionally, the number kited in the 2013 EAS consensus is hiked up another 25% by breaking with standard mathematical rounding.

EAS expert consensus, 2013
Through citation kiting, Benn et al appear to be a source for prevalence. Diagnosis continues the same de-emphasis of DNA testing, extensive family trees, and TG levels.

Benn, et al. 2012
Use Dutch screening criteria, but de-emphasize family pedigrees. Do not mention FCH and ignore high TG levels as exclusionary criteria, allowing not only FCH, but T2DM, Obesity, and METS to be confused with FH. FCH characteristics present a conspicuous bulge in the results.
1973 Goldstein's *distinction* between FH and FCH: 5 key points.

Dr. Joseph Goldstein and others studied extensive family trees of cardiac victims in an effort to segregate *genetically determined* events from *uninherited* events. They then studied the **type** of lipids involved for the genetically determined group. This resulted in the “delineat(on)” of “five distinct lipid disorders,” of which two will be key to understanding today’s patient swap. One lipid was cholesterol (LDL) and the other, triglyceride (TG). Those with high LDL and relatively normal TG were “the disorder easiest to detect, familial hypercholesterolemia.” On the other hand, those

### Abstract

To assess the genetics of hyperlipidemia in coronary heart disease, family studies were carried out in 2520 relatives and spouses of 176 survivors of myocardial infarction, including 149 hyperlipidemic and 27 normolipidemic individuals. The distribution of fasting plasma cholesterol and triglyceride values in relatives, together with segregation analyses, suggested the presence of five (distinct) lipid disorders. Three of these—familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia—were frequently observed. The combined disorder was shown to be genetically distinct from familial hypercholesterolemia and familial hypertriglyceridemia for the following reasons: (a) the distribution pattern of cholesterol and triglyceride levels in relatives of probands was unique; (b) children of individuals with combined hyperlipidemia did not express hypercholesterolemia in contrast to the finding of hypercholesterolemic children from families with familial hypercholesterolemia; and (c) analysis of

---

**1. Goldstein makes distinctions and “delineate(s)” the diseases FH and FCH.**

**2. Even before genetic identification, FH was clearly defined.**

**3. The distinguishing feature between FH and FCH is the presence or absence of *high* Triglyceride values.**

**4. The diseases are isolated with the aid of family pedigrees.**

**5. Diabetes mellitus can be confused with the inherited causes of high lipid levels.**

---

Hyperlipidemia in Coronary Heart Disease

**II. GENETIC ANALYSIS OF LIPID LEVELS IN 176 FAMILIES AND DELINEATION OF A NEW INHERITED DISORDER, COMBINED HYPERLIPIDEMIA**

Joseph L. Goldstein, Helmut G. Schrott, William R. Hazzard, Edwin Bierman, and Arno G. Motulsky with the technical assistance of Ellen D. Campbell and Mary Jo Levinski

*From the Departments of Medicine (Division of Medical Genetics, University Hospital, and Division of Metabolism and Gerontology, Veterans Administration Hospital) and Genetics, University of Washington, Seattle, Washington 98195.*

Familial hypercholesterolemia. The disorder easiest to detect, familial hypercholesterolemia, was characterized by the finding in relatives of a normal triglyceride distribution but an apparently bimodal cholesterol distribution. Segregation analysis suggested type IIb, type IV, or type V patterns. In the individual family with combined hyperlipidemia, the pedigree was often puzzling and confusing because of this variability in phenotypes. But, when the family data were extensive enough and lipid levels were measured in children, the disorder was relatively easy to distinguish from both familial hypercholesterolemia and familial hypertriglyceridemia.

Nonfamilial hyperlipidemias are often secondary to such factors as diet, alcohol intake, estrogen therapy, or to diseases such as diabetes mellitus, hypothyroidism, or nephrosis (3). In some cases, neither hereditary nor environmental factors may explain the high lipid levels, which are often encountered in patients with various types of neoplasms. Some patients have isolated hypertriglyceridemia (15) and others have the combination of both hypercholesterolemia and hypertriglyceridemia (3).
Two key steps to understanding the problem today: family pedigrees and triglyceride

Here are two important reminders when not relying on genetic matching: the importance of examining extensive family pedigrees and the role that triglyceride plays in making a distinction between FH and FCH. FH is noted both for its raised cholesterol but also for its relatively normal triglyceride. FH is typically not defined by the elevation of both lipids: cholesterol (LDLC) and triglyceride (TG). (We know that it is not impossible for an LDLR mutation carrier (FH) to also have a high level of triglyceride, but that is the exception and not the rule. If one finds the higher level of triglyceride, without the aid of genetic confirmation, the more probable diagnosis is FCH, not FH. More on this later.)

- Below left is a diagnostic flow chart demonstrating the steps in the delineation of FH and FCH, two of the five diseases presented in Goldstein’s 1973 report.
- Below right are two excerpts from the report. One (bottom) shows the criteria used in the classification of the diseases. The other (top) shows uninherited diseases, such as diabetes, with characteristics shared with FH and FCH.


Classification of hyperlipidemia in families. Classification of the lipid disorders was based on an analysis of the cholesterol and triglyceride levels among relatives of probands. In the absence of knowledge regarding the basic defects in the different hyperlipidemias, no method of sorting data for heterogeneity based on quantitative variation alone can be considered completely unbiased. However, in an attempt to minimize bias, the following approach was developed. Each of the hyperlipidemic families was initially separated into one of two groups depending on whether group A or not (group B) the family contained at least one relative besides the proband who would be considered unequivocally hyperlipidemic (i.e., whose lipid level was $\geq$99th percentile for adults of 20 yr of age and older or $\geq$95th percentile for younger individuals).3 Families in group A were further subdivided depending on whether the predominant lipid elevation in the family occurred in cholesterol alone (group A-1 or familial hypercholesterolemia), in triglyceride alone (group A-2 or familial hypertriglyceridemia), or in both lipids (group A-3 or familial combined hyperlipidemia). For the individual family this assignment to a specific group was determined by inspecting the pedigree and assessing the distribution of percentile values of the adjusted cholesterol and triglyceride levels. Analysis of one 11 member family is given for

- Probable Familial Combined Hyperlipidemia: Both cholesterol and triglyceride are often high.
- Probably Familial Hypercholesterolemia: high cholesterol but normal or less severe triglyceride.
- Consider unhinherited lipid disorder (“secondary,” “nonfamilial”) E.G., type 2 diabetes mellitus and others.
- If skip the examination of the family pedigree, I increase chances of misdiagnosing an acquired disease as an inherited one.
- Pattern of high cholesterol found in extended Family pedigree?
- Yes
- No

If I skip this step and neglect triglyceride levels in my diagnostic criteria for FH, FCH can be misdiagnosed as FH.
1973 Kahneman and Tversky; and inverting “Despite” and “Because”

Unravelling base rate fallacy is often counterintuitive, and thus a system which employs it can be assisted by human behavior and a delusion of “common sense.” Base rate gives us a probability from the outset, but irrelevant characteristics shared between two populations nonetheless provoke different and unjustifiable valuations attached to one but not the other population. For example, below, “evidence” of marital status does not distinguish Lawyers from Engineers. Truly distinguishing evidence, such as an authenticated university diploma, would help and would not be “worthless.” However, barring such uniquely distinguishing information, “evidence” can be shared or unshared between two populations. Or, to expose the same problem with different words, a characteristic can be sufficiently pervasive throughout both populations. In the text below, one who neglects the fallacy may object that Dick was rejected as a lawyer despite the fact that he shares characteristics with lawyers, even though the odds are clear that Dick is probably an engineer. One who embraces base rate would counter that Dick is rejected as a lawyer, because he merely shares characteristics with lawyers. (The illustration, rounded-box outline for text, and black box comments are mine.)

The subjects used prior probabilities correctly when they had no other information. In the absence of a personality sketch, they judged the probability that an unknown individual is an engineer to be .7 and .3, respectively, in the two base-rate conditions. However, prior probabilities were effectively ignored when a description was introduced, even when this description was totally uninformative. The responses to the following description illustrate this phenomenon:

Dick is a 30 year old man. He is married with no children. A man of high ability and high motivation, he promises to be quite successful in his field. He is well liked by his colleagues.

This description was intended to convey no information relevant to the question of whether Dick is an engineer or a lawyer. Consequently, the probability that Dick is an engineer should equal the proportion of engineers in the group, as if no description had been given. The subjects, however, judged the probability of Dick being an engineer to be .5 regardless of whether the stated proportion of engineers in the group was .7 or .3. Evidently, people

Example of a base rate solution: games 1 & 2

Here are two games, left and right, and we must choose to play one of them 100 times. After each game we restore the bins to their original types and quantities. The object is to end up with the item $T$ with the greatest degree of accuracy possible, which means that we also want to mitigate the chance of accidentally including $F$. Which game would we choose?

In the games, there are bins to draw items from or bins to put items into. These are represented by the rectangles with rounded corners. The contents in each bin are one or more of the following. There are True items, “$T$,” which have the characteristic, “$C$.” There are False items, “$F$,” which also have the same characteristic, “$C$.” Finally, there are items, “$N$” which do not have the characteristic “$C$” (and so by testing for “$C$” these “$N$” can be filtered out of the results).

For example, on the left, we draw from a bin of 100 items at random. $T$ would be selected, on average, about 2 in every 100 tries, but we would also mistakenly draw $F$, on average, two times. We end with two of $T$, but we also confused two of the $F$ with $T$, yielding a 50% error rate. On the other hand, in the game on the right, the error rate is only 2%.

What makes the difference between these two sorting systems?

In the diagram on the right, we begin with a toss of a coin. If the coin lands heads, then we draw from the left bin; if tails, then we draw from the right bin. Thus, there is a 50% chance of drawing from the first bin, which gives us $T$. (To bring this back to FH, this represents the fact that 50% of those who are first degree relatives of verified mutation carriers will have the mutation.) On the other hand, 50% of the coin tosses will land tails, where we then randomly draw from the bin full of 100 items and where at this point our chance of drawing $F$ is only 2%. Drawing from these first two bins 100 times according to the flip of a coin, we end with 51 $T$ to 1 $F$ on average, but diluted by the presence of $N$. This dilution with $N$, in both games, is resolved in an exclusionary step: we see that there is a characteristic which distinguishes $T$ and $F$ from $N$. That is $C$. After we remove all those with characteristic $C$, we end with a more concentrated pool. The game on the right is more accurate than the one on the left because we can get $T$ with a flip of a coin. (As for FH, this is the same as finding a verified mutation carrier and then beginning with a first degree relative. Because this relative has a 50-50 chance of carrying the mutation, we begin with a superior “prior probability,” and we’re successful 50% of the time with the first step alone.)

What makes the difference between these two sorting systems? On the right, the odds of $T$ is 1 in 2. All things being equal, beginning with a strategy that employs base rate is vastly superior to a strategy which employs base rate fallacy – unless you seek to profit from the error. (Of course, to perfectly replicate a genetic inheritance scheme, I would need to add in the fact that there are two parents, each with two alleles, and so on .... However, we are not making a point about genetics here, but mathematics, so for the most part, we’ve stripped down the genetic backdrop in order to isolate a single mathematical problem at center stage: Base Rate Fallacy. I invite the reader to add elements representing a more complete diagram of inheritance and then make the relevant adjustments to the probabilities. Although some of the numbers will change, the greater contribution to the difference between results will lie with base rate.)
1993 Understanding Base Rate Fallacy: Bringing Goldstein and Brown together with Tversky and Kahneman.

Dr. Roger Williams et al employed base rate to great success: beginning with first degree relatives of known carriers. In such a pool, a person with 310 total cholesterol has a 95% chance of carrying the mutation, whereas if we simply begin with the general population, the chance is under 4%. Note Williams’ comment that the “clinical clues are weak predictors of FH.” This is because these same “clinical clues” are shared with many other diseases besides FH. For example, high cholesterol is the dominating “clinical clue” both in FH and FCH scoring systems, while the only uniquely distinguishing characteristic for FH is the presence or absence of the LDL Receptor mutation. Barring genetic testing, if we tally up a score based mostly on cholesterol levels, we cannot overcome the fact that passing scores are shared among both on-target and off-target populations. To bridge the divide between ideal-but-impractical genetic screening and the high error rate in the scoring systems, this third option was suggested by Dr. Roger Williams, employing the advantage of “a priori probabilities.” To recap the movement toward precision medicine, first there were “clinical clues” to distinguish FH from other diseases, such as FCH (e.g., exclude those with high triglyceride), then we advanced to genetic testing for the LDLR mutation, and then, due to the impracticality of testing entire populations, Dr. Williams employs a base rate strategy. (By design, the numbers used in the games are not representative of the numbers relevant to FH prevalence. The sole purpose of this illustration to isolate the difference between the mathematical systems, not any given quantity within a given application. One system is biased: “those with characteristics shared with FH are therefore FH.” The other acknowledges base rate and takes advantage of a superior prior probability.)

1993 Williams, et al
DOI: 10.1016/0002-9149(93)90155-6

### Diagnosing Heterozygous Familial Hypercholesterolemia Using New Practical Criteria Validated by Molecular Genetics

Roger R. Williams, MD, Steven C. Hunt, PhD, M. Catherine Schumacher, MD, Robert A. Higdon, MD, Mark F. Lopetig, MD, Ewan H. Ledingham, and Paul N. Hopkins, MD

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<th>TABLE 1 Percentages of Adults Age 40 Expected to Have FH According to Cholesterol Level and Disease Relative of FH</th>
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<tr>
<td>familial</td>
</tr>
<tr>
<td>nonfamilial</td>
</tr>
<tr>
<td>total</td>
</tr>
</tbody>
</table>

Assessing familial hypercholesterolemia risk in clinical settings: Physicians often perform informal assessments of a patient’s risk using standard clinical information. High cholesterol, early coronary disease, and a positive family history of early coronary disease are clinical clues thought to suggest FH. However, these clinical clues are weak predictors of FH compared with the cholesterol criteria presented in Tables I to III.
1993 Williams: watching out for FCH when identifying FH.

Below are excerpts from Dr. Williams’ 1993 paper. Besides base rate, another important take-away is the importance of making a distinction between FCH and FH – otherwise one will misdiagnose the FCH as FH – and treatments tailored to the respective diseases will be missed. FH for example tends to require more medication than FCH, (see item 10 below), and FCH responds better to exercise (see item 8 below). And let’s not forget that “diagnosis,” by definition, is an attempt to distinguish between diseases. Again, barring genetic confirmation, the most probable distinguishing feature between FH and FCH is the presence or absence of elevated triglyceride. But Dr. Williams goes further and leaves us with other important characteristics which value the differences, not the similarities, between the diseases. Appropriately, the similarities are presented as warning signs, not identification criteria. Because the two diseases share many of the same characteristics, we are warned against confusing one with the other. With the complete set of premises below, we can not say, “The FCH are rejected from a diagnosis of FH despite the fact that they share the same characteristics.” Stressing “shared characteristics” is the problem. For example, both FH and FCH run in families and both involve high cholesterol – both are characteristics which score on FH diagnostic systems recommended by today’s Pharma-funded “research.” As we shall see, by replacing this emphasis on distinctions with a later emphasis on similarities, FCH will be diagnosed as FH. To fast-forward to the end of my presentation, see pages 57 and 58.)

1. FCH prevalence is higher than that of FH. Thus, of those passing a scoring system in which cholesterol levels dominate, the FCH will predominate over the FH – if we simultaneously avoid distinguishing characteristics. FCH would appear to be “FH,” and it would appear as though FCH prevalence had increased.

2. What happens if later FH recommendations omit triglycerides from exclusionary criteria? This is an essential, distinguishing feature between FH and FCH. What if we omit mention of FCH altogether?

3. These two features do not separate FH from FCH. Stressing the shared characteristics, FCH can look like FH.

4. Note that diabetes and obesity have a closer association with FCH than with FH.

5. Note that FH patients predominate at the highest level of cholesterol, while at a notch below that level, the ratio inverts and FCH predominates. Later, we will see the vestige of misdiagnosed FCH through a “bulge” at this next lower notch within statics of those said to be “FH.”
2005 & 2010: Overlap between FCH, METS, T2DM, and Obesity
As Williams observed, FCH characteristics overlap with characteristics of diabetes and obesity more so than FH characteristics do. On the left, Cennaro et al depict an association of combined hyperlipidemia with, as the name suggests, familial combined hyperlipidemia, but also with type 2 diabetes and metabolic syndrome. As can be seen, higher TG levels often distinguish these others from FH. So a scoring system that de-emphasizes high TG levels or does not exclude those who have such will support an erroneous assumption that many with high cholesterol are "FH" even if their cholesterol levels are due to other causes. Also, FH problems show up in childhood more so than FCH problems do -- for that reason, a scientist can remove a degree of risk of misdiagnosis when studying only children (see page 16). On the right is a report about lipid disorders in childhood. A distinguishing feature between FH and the otherwise similar lipid profiles of FCH, METS, and obesity is high TG. Again, if we deliberately preclude or discourage genetic testing, and deliberately remove consideration for higher TG, we will decide for future students who the "FH" patients are. If no one has an awareness of the historical record, having thus no hint of the missing information, then the new, re-written instructions support higher prevalence estimates and help increase drug sales.


FCH is associated with METS, T2DM, and Obesity

Is not characterized by high TG.

Are characterized by high TG.

Causes of combinations of high TC and high TG are METS and FCH. Obesity can also accompany high TC and TG. T2DM also comes with high TC.
2006 Van Aalst-Cohen tests the scoring system

Dr. Emily Van Aalst-Cohen set the scoring system results against the DNA standard. How accurate are these scorings systems? Her team "used a set of established clinical diagnostic criteria to define FH." They then examined this group genetically. In how many would they find mutations? Out of 2,400 that surpassed their threshold for "FH," a mutation was found in 1,255, and no mutation was found in 1,145. This is pretty close to the flip of a coin. As already known and warned against by Goldstein, Williams, and others, the LDLR mutations express themselves in a variety of profiles so extreme that a scoring system cannot separate mutation carriers from those who suffer from other inherited and uninherited lipid disorders.

Extensive family pedigrees and keeping an eye out for FCH are imperative. Of particular concern, and underscored by Goldstein, Williams, and Van Aalst-Cohen, are the FCH. In the screenshots below, the mutation carriers are the "LDL-R plus" and those in whom a mutation was not found are the "LDL-R minus." The difference between their respective sets of numbers is consistent with the presence of FCH and non-FH in the LDL-R minus group. Note the differences between LDLc and triglyceride levels, with the reminder that LDLc values dominate within an FH definition, while triglyceride levels dominate within the FCH definition. (Note the bump higher in diabetes for the FCH; this will come up again later.)
It is very clear in 2009 that the original hope for “precision” medicine by way of genetics has arrived, but only if we stick with genetics. If we return to the old method of scoring circumstantial evidence, while the *forensically decisive* method of *genetic matching* is available, we go backwards, whether by the failure to educate the next generation of researchers or by the success of a publication strategy to obfuscate the information. It is this latter case that I am making with my current research. The key point between the scoring systems and genetic matching is the fact that “no single diagnostic criterion” will get the majority of genuine carriers and also exclude the majority of non-carriers. This is a problem for the scoring systems, and when they are employed, one accepts the abandonment of the majority of carriers. (See Fhprevalence.com.) Nonetheless, in concentrating the most serious cases, a serious attempt to *exclude* the FCH, T2DM, and other causes of high LDLc must be made. If not, then the other diseases will be mistaken for FH.
2011 From Van Aalst Cohen to Van der Graaf: a question

Is the failure to find an FH mutation due to the fact that scientists have not yet discovered all mutations? This much-used argument in industry-funded papers today begs a very important question. The failure to even bring up the neglected question of misdiagnosis is telling. Dr. Van Aalst Cohen provided strong evidence that the presence of the FCH in FH scoring results is probable, but could not eliminate the underlying question: do we know the majority of mutations accounting for FH? Five years later, with more mutations having been discovered and greater technology at her disposal, Dr. Anouk Van der Graaf tackled precisely this same issue, but with a clever strategy: focusing on children precludes a greater part of the non-FH and the FCH. FH tends to reveal high LDLC from the outset of life, whereas acquired LDLC disorders and FCH as well tend to reveal high LDLC much later in life. By restricting her study to children Van der Graaf precludes a large number of non-FH and the FCH from the scoring system results at the outset. Using an “unequivocal” diagnosis of FH, but after precluding a majority of the Non-FH and FCH, how many “large effect” mutations are as yet unaccounted for?
2011 Van der Graaf: No mutation = probable misdiagnosis.
Again, FCH is implicated in the failure to find mutations within an FH scoring system’s results. The problem is that these scoring systems are really just epistemological cousins of what in legal arenas serve as weaker forms of circumstantial evidence. Just because two suspects share the same characteristic does not mean that both or either are guilty. This problem can also be understood through Kahneman and Tversky’s analysis of human bias and base rate (see pages 9 and 10). If there is only one bank robber on video and he wore red shoes, then it would not be wise for me to declare that there were two robbers just because I found two people with red shoes. *Finding shared characteristics with a target does not alter the actual population of that target.* Having two suspects and only one bank robber, a process of exclusion is imperative, *if I value few-but-accurate over many-but-inaccurate.* Lowering the standard of accuracy increases the quantity of suspects to two, even though the video establishes the odds at 50%. If both FH and FCH have passing scores, have I really doubled FH prevalence?

The FCH were in large part precluded from the study by excluding adults. The hit rate was 95%. Thus, in other studies, a large portion of those in whom a mutation could not be found most probably suffer from other diseases, like FCH.

Without responsible exclusionary criteria the results of a diagnostic procedure will be equivocal.

Consistent with FCH and environmental factors. 

**Discussion**
In a large group of referred children with a strictly defined phenotype of ADH, we were able to identify 77 different functional gene mutations in 95% of cases. We therefore demonstrate that in almost all children the ADH phenotype can be explained by mutations in genes that are currently known to underlie this syndrome.

Our results have a number of important implications. First, detection rates in our patients are much higher than reported by our colleagues. They assessed mutation detection rates to establish the clinical utility of diagnostic tools and found them to vary widely from 20% to 90%. On the basis of these data, claims were made that a large proportion of ADH is still unexplained. We strongly disagree with this contention on the basis of the present study. The discrepancies between our data sets and the others could be explained by the rigorous criteria we used to select for ADH. In fact, earlier studies also demonstrated better detection rates when a more stringent definition of phenotype was applied. Furthermore, the thorough molecular analyses of the *LDLR*, *APOB*, and *PCSK9* genes, including splice-site sequencing and detection of large deletions and insertions, might provide additional reasons for the higher detection rate in our patients.

2011 Van der Graaf
DOI: 10.1161/CIRCULATIONAHA.110.979450

and renal function. From this population, we selected only patients with a clear clinical phenotype of ADH. This was defined as an LDL-C level >95th percentile for age and gender and autosomal dominant inheritance pattern of hypercholesterolemia, ie, at least 1 biological parent on treatment for hypercholesterolemia and a family history of hypercholesterolemia and cardiovascular disease. Because physical symptoms are rare in children, we did not consider this an inclusion criterion. Exclusion criteria were thyroid dysfunction, nephrotic syndrome, autoimmune disease, liver disease, primary biliary cirrhosis, and obesity. For this study, we chose a body mass index (BMI) cutoff at the 75th percentile for age and gender because it has recently been shown that at a BMI of above the 80th percentile, significant abnormalities in cholesterol levels begin to occur in children.

**Lipids and Lipoproteins**
Although in both groups the mean total cholesterol and LDL-C levels were well above the 95th percentiles for age and gender, hypercholesterolemia was less pronounced in the group without an established gene mutation compared with those with a molecular diagnosis, with an LDL-C of 4.40±0.48 versus 6.13±1.53 mmol/L (P=0.001), respectively (Table 2). This difference remained significant after
The outside walls of a room can be diagrammed and tell us something of the room inside. It’s not perfect, but it does give us some information. Likewise, Goldstein drew sharp lines between the diseases FCH and FH, while at the same time warning the reader that they can be confused with each other. In a sense, we can focus on FCH as if it were a wall that can tell us something about the FH on the other side. So, here, let’s look at a modern definition of FCH – by the very EAS group guilty of citation kiting in the industry’s Authoritative reports (pgs. 26 and 29).

doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemia, European Society of Cardiology (ESC) and European Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano (Chair), Ian Graham (Chairperson) (Ireland), Guy De Backer (Belgium), Mats Johansson (Sweden), M. John Chapman (France), Heinz Drezel (Austria), Arno W. Hoes (The Netherlands), Caterina S. Jennings (UK), Terje R. Pedersen (Norway), Zhijie Reiner (China), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), Vigerskij (The Netherlands), Charalambos V. Vlachopoulos (UK), Jose Luis Zamorano (Spain)

All dyslipidaemias must be represented. This is where the story falls apart. With side-by-side facts, reconciliation is available. FCH must be mentioned along with FH.

9.1.1 Familial combined hyperlipidaemia

Familial combined hyperlipidaemia (FCH) is a highly prevalent dyslipidaemia (1:100) and an important cause of premature CAD. FCH is characterized by elevated levels of LDL-C, TGs or both. The phenotype varies even among members of the same family. FCH shares considerable phenotype overlap with type 2 diabetes and MetS. FCH is a complex disease and the phenotype is determined by interaction of multiple susceptibility genes and the environment. The phenotype even within a family shows high inter- and intraperson variability based on lipid values (TGs, LDL-C, HDL-C and apoB). Therefore, the diagnosis is commonly missed in clinical practice: the combination of apoB >120 mg/dL + TGs >1.5 mmol/L (133 mg/dL) with a family history of premature CVD can be used to identify subjects who most probably have FCH. (296) Currently, research is ongoing to define genetic markers: hopefully this approach will facilitate diagnosis of this frequent genetic dyslipidaemia.

The concept of FCH is also valuable clinically in assessing CV risk. It emphasizes both the importance of considering family history in deciding how rigorously to treat dyslipidaemia and that elevated LDL-C levels are riskier when HTG is also present. Statin treatment decreases CV risk by the same relative amount in people with HTG as in those without. Because the absolute risk is often greater in those with HTG, they may therefore benefit greatly from hypocholesterolaemic therapy.

There are more FCH than FH.

Like FH, high LDL-C, but unlike FH, FCH can have higher TG.

Environment plays a strong role. There are lifestyle changes that can help.

If genetic markers would facilitate FCH diagnosis, why doesn’t the superior genetic clarity with FH dominate FH diagnostic strategies?
The Fall of precision medicine: An explicit equivocation strategy, where FCH is the real target.

Dr. Seth Baum’s Exclusionary Criteria is MEDPED: 2014 vs. 1993-1996

Dr. Seth Baum was paid the most money from Aegerion for promoting its product to other doctors... and to investors. Aegerion was and still is under intense federal scrutiny, despite the $40 million-dollar settlement with various federal agencies. Now Dr. Baum receives payment from Amgen. In 2014 Dr. Baum explained an “evolution of a definition” of FH and actually proposed a “language strategy.” There is the discouragement of genetic testing, but the assault on Williams’ solution to base rate fallacy is the first point I will make about this industry-funded reversal toward imprecision medicine. Dr. Williams’ use of prior probabilities when identifying FH was known as MEDPED. Dr. Baum devalues and discourages use of the original MEDPED system. And he does so by misrepresenting the historical record. It is easy to do because working with prior probability is so counterintuitive it remains invisible as the first step of a two-step procedure. In truth, after establishing the first step of enriching prior probability, the second step is to check LDL-C levels, and this sequence yields more efficient results. Unfortunately, the idea of overcoming base rate fallacy is now lost and replaced with the default of the fact-ectomy: the now unimpeded employment of the fallacy.

1996 MEDPED Williams et al

MED-PED: An Integrated Genetic Strategy for Preventing Early Deaths


Table 2. Validated criteria for the diagnosis of heterozygous familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Age 40</th>
<th>Age 30</th>
<th>Age 20</th>
<th>Under 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Very high total cholesterol:</td>
<td>&gt; 360/63, &gt; 340/88, &gt; 320/70, &gt; 270/70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Normal triglycerides:</td>
<td>&lt; 200/15, &lt; 180/10, &lt; 150/7, &lt; 100/4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or very high LDL cholesterol:</td>
<td>&gt; 260/63, &gt; 240/62, &gt; 210/54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. No secondary cause of high cholesterol (nephrotic syndrome, pregnancy, etc.)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>d. At least one pediatric relative (child, grandchild, niece or nephew, etc. &lt; 18 years of age with very high cholesterol (total cholesterol &gt; 270) OR at least one close relative with tendon xanthomas.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>e. Dominant expression in the family:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>… about half of siblings and offspring affected.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bimodal (clear separation between normal and abnormal in relatives)</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

4. Among close relatives of confirmed FH index cases use these criteria:

(Both criteria must be met) | Age 40 | Age 30 | Age 20 | Under 18 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. High total cholesterol:</td>
<td>&gt; 300/63, &gt; 280/72, &gt; 240/62, &gt; 220/57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or High LDL cholesterol:</td>
<td>&gt; 219/56, &gt; 195/50, &gt; 175/45, &gt; 165/43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. No secondary cause of high cholesterol (nephrotic syndrome, pregnancy, etc.)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Some functional mutations of the apolipoprotein B locus (e.g., apo B 3500) have similar consequences on LDL cholesterol and early coronary heart disease. These are often referred to as "familial defective apo B" or "FDB". Some MED-PED registries are also including persons and families with FDB in their efforts to find and help persons with FH.
Contrasting 1997 Leren with 2011 Goldberg: the pivot from precision to imprecision.

In 2011, Dr. Baum was a peer reviewer with the journal that published the 2011 report. The lead author of the 2011 paper was Dr. Anne Goldberg. Observing the shift from the singular to a plural usage of “FH” renders the language strategy conspicuous. What underlies the category heading for the entire group of lipid disorders becomes “FH” in 2011. The subcategory, familial hypercholesterolemia, becomes the category heading, familial hypercholesterolemias. Now “familial hypercholesterolemia” in the title in Goldberg’s series is not synonymous with many of the references to “FH” within the article. The title, being singular, and having that definition established over the prior decades, we are referring to the LDL Receptor, but the actual text equivocates “FH,” which thereafter refers to an entire group. The use of “FH” will flicker back and forth from the category heading of a group to the specific disease caused by a mutation in the LDL receptor. However, the 2011 Merck Manual, updated by the same Dr. Goldberg, is not limited to FH and must list the diseases separately.

The explanation for the failure to diagnose and treat FH patients may be in part due to the vague clinical diagnostic criteria that are being used. These criteria often make it difficult to distinguish FH from other hypercholesterolemias. A more specific diagnostic criteria for demonstration of a mutation in the LDL receptor gene that causes a functionally abnormal LDL receptor is necessary.

The FH on the right includes the misdiagnosed on the left.

Goldberg’s series of FH is not synonymous with many of the references to “FH” within the article. The title, being singular, and having that definition established over the prior decades, we are referring to the LDL Receptor, but the actual text equivocates “FH,” which thereafter refers to an entire group. The use of “FH” will flicker back and forth from the category heading of a group to the specific disease caused by a mutation in the LDL receptor. However, the 2011 Merck Manual, updated by the same Dr. Goldberg, is not limited to FH and must list the diseases separately.

For the 2011 Merck Manual, Dr. Goldberg keeps the diseases separate. For the 2011 series funded by Pharma (center), they are all conflated under familial hypercholesterolemia and the acronym, “FH.”

Left center, Goldberg defines FCH as “FH.” Above, the two are defined in the Merck Manual as separate diseases.
2011 Language Strategy includes FCH

FCH is subsumed under a newly broadened definition for FH. We’re altering the definition of FH from the receptor mutation itself to the whole receptor pathway. But even that expansion does not include FCH. This is confirmed by the fact that prevalence of FCH is 1/100, whereas lumping the APOB, PCSK9, along with the LDLR mutations comes out to the 1/300. If FCH were included with the new definition of “FH,” prevalence would be around 1/74—an absurdity. Appropriately, there is no mention here of high triglyceride as a red flag for FCH—being consistent with the definition of FCH and the feature that distinguishes it from FH. But when FCH and high triglyceride are mentioned, it is under the assumption that the FCH are FH. This is new and revealing. Also, 1 in 1,000,000 million homozygous is calculated through Hardy-Weinberg’s equation from the heterozygous’ 1/500, but we arrive at those rates only if we limit our FH definition to the LDLR mutations. On the other hand, the heterozygous can only be 1/300 if we add in the APOB and PCSK9 mutations. So, below, the FH in HoFH is limited to the LDLR mutations, while the FH in HeFH adds in the APOB and PCSK9. (As we will see later, HoFH will be re-defined to include the APOB and Compound Heterozygous FH.)
The Merck Manual in 2018: double-counting the APOB and PCSK9

In 2011 and 2018, Goldberg does not linguistically conflate the components in the Merck Manual, but in 2018 the quantities for APOB and PCSK9 are double-counted. In the 2011 JCL series by Goldberg, adding the “s” at the end of the word -- IE, making it “familial hypercholesterolemias” -- left the inclusion of the APOB and PCSK9 technically true. The only way to double “FH” prevalence was to conflate the diseases in this way. This was a large factor in moving the prevalence from 1/500 to 1/200 or 1/300. Any good reason for doing this however was lost in the next move: in the 2018 Merck Manual, Goldberg still kept the diseases separate, listing the APOB and PCSK9 separately, and specifically defining the FH by the LDL receptor. Nonetheless, she kept the APOB and PCSK9 quantities inflated in a prevalence devoted solely to LDLR mutations, “FH.” In actuality, the only support for an FH prevalence of 1/200 or 1/300 involves sneaking in the APOB and PCSK9 carriers. But they are clearly listed separately here. The linguistic conflation was explicitly declared in the 2011 series led by Dr. Goldberg. However, if we unpack that conflation here, we must also unpack the quantities of the components. The APOB and PCSK9 are double-counted in 2018.
Daniel Rader leaves the issue clear

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

The recent Pharma-funded effort is more aptly called a linguistic strategy than a prevalence study. “Higher than expected” prevalence is necessary to increase the alarm of “underdiagnosis.” It is the key point within the publication strategy. And it is a false claim.
Kiting for Prevalence and “Urgency,” FH is Defined Genetically

2013 EAS: Citation Kiting – Norwegian report involving the confusion of FCH with FH

A pattern is revealing itself. Citation kiting once again assumes the FCH into the FH count. The confusion over Heiberg began earlier than the 2013 EAS report. However, it is here clearly taken up and presented to mainstream academia. On the left is the highly influential, 2013 EAS report by Nordestgaard, et al. It claims that prevalence in Norway was estimated to be 1/300 and used that number to undermine the standard 1/500. It cites Heiberg and Berg’s 1976 paper as the source for this claim, bottom right. However, that 1976 source clearly puts FH prevalence at 1/455. The 1/300 is for FH and FCH together. This exposes a plan, not just to inflate the prevalence, but to bring in the other disease, FCH, as FH. This relatively obscure paper with its past of checkered citations is now an opportunity for big-league citation kiting. However, as with all deception, the refutation of Nordestgaard’s use of Heiberg’s estimate is very crisp: one of the very authors of this 1976 report, K. Berg, is quoted in an interview – top right of illustration – citing his own 1976 report and putting the prevalence at 1/500.
Leren’s 2011 papers frame the shift made by Goldberg, et al, in 2011

Mid-year 2011, Leren shifts prevalence and APOB classification while using the same source that he used before: Heiberg. This is a sudden shift out of the flow of the established cultural inertia. A conflation identical to Goldberg’s in America shows up in Norway, at the same time. I cannot rationally declare with certainty that this is more than a coincidence, but I can say that it is suspicious. In the 2011 Goldberg series, with heavy pharma funding present, prevalence is 1/300 and “FH” is unceremoniously assumed to include the FCH. What are the odds that (1) the Heiberg numbers would slip off of 1/500 to land on 1/300, (2) by including the FCH in the total for FH – without explanation – (3) chronologically bracketing Goldberg’s unprecedented use of 1/300.

Thereafter, Leren’s FH is as much as 1/300, which is only possible with Heiberg if one counts the FCH as FH.

Pre-Goldberg:
1. Prevalence is 1/500.
2. Heiberg at 1/500 assumes FCH is not also FH
3. APOB are not FH.

Post-Goldberg:
1. Prevalence shifts to 1/300.
2. Heiberg at 1/300 assumes FCH is also FH.
3. APOB are now said to be FH.
More 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. I found many shenanigans in these reports. (See fhprevalence.com for more detail.) For the present purposes, we’ll just 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. Adding up 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, see my reconciliation of the Danish reports at fhprevalence.com and page 28.)

Citation kiting forces new math. This is not epidemiology.
There is no external, contemporary source for the doubled prevalence in the 2013 EAS consensus report. What concerns us here is the citation trail. The 2013 EAS paper did no prevalence study of its own. This Authoritative report did not even use the results of the study it cited. Consequently, there was no external, contemporary source in this Authoritative report for the new result and new criteria. The only source to the corrected prevalence rate is a “self-citation” within this very, selfsame, Authoritative report, found in a caption to an illustration, referring to a “personal communication” with the lead author: Borge Nordestgaard. Did someone actually talk to him? … or did he simply talk to himself? This is a multibillion-dollar industry. And the new prevalence and new criteria rests on a personal communication, with the selfsame lead author? This report has no external, contemporary source for the doubled prevalence. From here on the Authoritative report is usually cited in the industry as if it were the source itself. (The 2012 report on the left is contradicted by a paper in 2016, by the same authors, using much of the same study population. See fhprevalence.com and page 28.)
The reconciliation of the 1st and 2nd Danish report procedures, a summary

See FHprevalence.com for the full report.

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.
Transparent Citation Kiting in the 2014 EAS “consensus”
I’ve discovered that 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” and to the publisher’s failure to reconcile the value claimed with its actual source as “citation kiting.” We’ve seen this sort of “fact-ectomy” in the linguistic manipulation of the definition of “FH” and across the Danish and 2013 EAS “consensus” reports. (See fhprevalence.com.) 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 a table of parallel definitions and values. What we see is something like a relay team that cheats by switching batons, instead of passing on the original. (In the following pages, we’ll see that HeFH is actually 1/500, not 1/319.)
Prevalence of 1 in 1,000,000 is confirmed, not overthrown

Is there a good reason for blending different diseases under the name of one of them? Compound HoFH will soon be HoFH. What happens when we hold to the historical record, and tease the underlying components out from their new, elastic 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 in the refutation. Prevalence for HoFH was 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: Yet the number

“16” as an explicit reference to HoFH is nowhere to be found in the entire report, nonetheless it is clearly employed in off-text calculations. And this report is on the homozygous, yet a prevalence number devoted to the true homozygous FH is not in the text. True HoFH in this report actually comes out to 1/1,045,149, astonishingly close to the established 1/1,000,000. Through the very Hardy-Weinberg equilibrium employed by the authors, 1/000,000 HoFH is 1/500 HeFH. Yet this true HoFH result will not be mentioned, not here, not in the 2014 EAS. The 2014 EAS will brazenly take the HoADH and simply call them HoFH, and HeFH will be printed as 1 in 244.


1st page, readers are misled into thinking that results are derived from 20 homozygotes.

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

2nd and 3rd pages, 4 are removed from the results. Thus, 20 raw hits minus 4 biased hits equals 16 unbiased HoFH.

Results

and 4 homozygotes for APOB mutations (hoFDB) (Table 1). Four hoFH patients from two different families were offspring of consanguineous parents. No compound heterozygous APOB or

By not blending the diseases and by using simple division, HoFH is confirmed to be 1 in a million. The homozygous are the main interest of this report and future reports will cite this result for HoFH and yet its prevalence is not printed ... at all. What is printed is clearly HoADH.
Just plain old bad math — inflates a multibillion dollar market estimate for investors
I believe that “16” is nowhere to be found in the Dutch report because it would render HoFH prevalence readily available to simple division, proving the Nobel Prize winners’ original estimates. (The Nobel Prize winners are now on Regeneron’s board.) But in the roundabout path taken to avoid this, someone slipped with the final result. As hard as this is to believe, in a multibillion-dollar market for FH, with a mathematical task one learns in elementary school, the numbers presented in plain sight just don’t add up. Literally. They are really big numbers, that is true, but the task is the simple addition of fractions. Not only does this error get past peer review in the Dutch paper, but it is reprinted in the 2014 EAS ... which is now widely cited. This 1/300,000 is printed by Novelion and Esperion in their SEC filed annual reports. It is wrong. The number is even cited within the FDA. It is as if someone put together an error and sent it on autopilot, to glide on through medical, investor, and regulatory literature, never touched by human examination. That’s part of both the cause and the effect of citation kiting: what we don’t examine endures as a perfect illusion of “science.”

Math: The result is 1/400,000, not 1/300,000. The basic math in the Dutch report literally does not add up. This **erroneous** result is carried over to the widely broadcast 2014 EAS report. With citation kiting this error has spread for 6 years and counting. Since citations are cited and not sources, very few readers make contact with the actual math, however basic. This error is even cited by the FDA.

In the current analysis, we established the prevalence of molecularly defined hoADH as 1:300,000 (1/407863 hoFH/compHeFH + 1/180597 hoFDB) inhabitants in the Netherlands, which is at least three times more frequent as previously described. The prevalence

Linguistics: The “HoADH” result added in CompHeFH and HoFDB alongside HoFH; it is not synonymous with HoFH. Through citation kiting, this total will be renamed in the 2014 EAS as HoFH. And here it is in an SEC filing.

2017 Novelion 10-k

Estimated Prevalence of HoFH

There is no patient registry or other method of establishing with precision the actual number of patients with HoFH in any geography. Medical literature has historically reported the prevalence rate of HoFH as one person in 1,000,000, based on an estimated prevalence rate for HoFH of one person in 500. Analysis of HoFH prevalence has been evolving in recent years culminating in published medical literature that suggests that the actual prevalence of both HoFH and HoFDB may be significantly higher than the historical estimates. For example, in 2014, the European Atherosclerosis Society (“EAS”) Consensus Panel on FH published an article citing research that would result in an estimate of the prevalence of HoFH in the range of between one person in 300,000 and one person in 160,000 or 3.33 persons per million to 6.25 persons per million, which is consistent with estimates that can be derived from other publications from the last few years. The FDA cited this estimate in its review of PCSK9 inhibitor products in June 2015. There is no
If the Math is deemed correct, by the authors’ own admission the Dutch result would be biased

Review: those whose parents’ marriages were consanguineous have been left in the text – but only for the introduction – and perhaps for an off-text equation for the final result. On page 1, in “methods and results,” numbers are provided that result in 1/300,000 ... but only if one does not scrutinize the rest of the paper. The HoFH count on page 1 is not the HoFH count used in calculations used for results on page 3. 20 true homozygotes are declared in the introduction on the first page, but 4 are subtracted on page 2 because including them “would inflate the prevalence.” But reinserting those 4 back into the results is the only way to reach 1/300,000 on page 3. This is not printed in the text, and so the math can only be considered “correct” if one accepts that the 4 explicitly removed due to bias are later reinserted in an off-text calculation. The authors say that the 4 would inflate the results, and here we see that 4 is used for the results, off-text. There will be more who read the introduction’s “methods and results” than who will scrutinize and question the actual methods and final results found in the full paper. The 2014 EAS report prints this admittedly biased result. The fact that there were 4 APOB carriers added and 4 from consanguineous marriages subtracted complicates the analysis, but not the result: we’ll get 1/371,608 two different ways, with consanguinity but without the APOB and with the APOB but without consanguinity. Either way, restoring textual integrity, 1/300,000 does not add up.

2011: Founder Effect precludes comparison of the Netherlands’ population with the general population of the USA

Briefly, founder effect results in an unusual prevalence due to specific conditions and cannot thus be representative of a usual, general population like that of the USA. Dutch researchers, using data from the StOEH screening program, found evidence of founder effect in the Netherlands (left). We will then see some of the same authors, using the same data from StOEH as if representative of the general population (right). With “gerrymandering,” politicians are able to select precisely those geographical boundaries which favor their own prospects. I’ve coined the word, “geno-mandering,” to illustrate how pharma has funded researchers who have selected precisely those geographical boundaries which favor pharma’s own prospects. (The Danish reports exploit the intermediate founder effect in Denmark, and Regeneron will later take advantage of founder effect among the Amish in its 2016 study.) (Red Flag: the 2014 Dutch report shows up in the 2012 annual report for StOEH: See online PDF: “JAARVERSLAG 2012, STICHTING OPSPORING ERFELIJKE HYPERCHOLESTEROLEMIE.” That is line of research, however, for another time.)

On the left, proof of a genetic anomaly in the Netherlands: founder effect. FH in the Netherlands is a special study, with higher than usual prevalence.

On the right, the claim that the Netherlands’ FH prevalence is relevant to the rest of the world. Both papers use the same data source: StOEH. (This 2014 Dutch report is cited in the StOEH 2012 annual report.)

Even though the 2014 Dutch report shares 3 authors, it’s as if founder effect is not present in the Netherlands. (4 authors in the 2012/2014 Dutch report will appear in the 2014 EAS report.)

the heterozygous ADH cases. The true prevalence of heterozygous ADH might even be higher, which would be in line with data from a recent Danish study that reported a prevalence of 1:137.22

It should be noted; however, that, for this Danish study, clinical ADH criteria were used, which is a combination of lipid levels, clinical symptoms, and family history. The Dutch population is an open society and we used a strict model to estimate the prevalence of hoADH. As a consequence, these data could probably be extrapolated to other societies in Europe and the USA.
Founder effect and Regeneron: Geno-mandering -- epidemiologists have taken a page from political Gerrymandering

- **Gerrymandering** is where politicians have the power to draw the borders around precisely those voting districts which maximize the outcome of a future election in their own favor.
- **Geno-mandering** is where researchers have the power to draw the borders around precisely those geographic regions which maximize prevalence of a genotype in the favor of Big Pharma.
For locating people for drug sales, genetic testing is demoted to the lowest priority
Both the heterozygous and homozygous FH were originally defined by the presence of the LDLR mutation. Through a decade of citation kiting, FH has transformed one of the best understood diseases into one of the least understood. Williams’ “clinical” diagnostic system came with a base rate advantage, and this advantage has not been carried forward as the leading screening strategy in the USA since his tragic death. Recent federal action exposed Aegerion’s strategy of avoiding precise definitions of the disease. Even the peer-reviewed diagnostic criteria have been engineered by way of fact-ectomies carried forward through the citation kiting, and through such, we can observe the art of redefining FCH, T2DM, METS, and the obese as “FH.” Although it had already been established that genetic identification of an LDLR mutation was the only unequivocal diagnosis, a truncated diagnostic procedure is proposed today, and genetic testing is discouraged. Now, Aegerion’s 10-K says that there is no consensus on diagnostic criteria. But what should we expect after nearly a decade of equivocating the definition and diagnostic procedure by way of citation kiting? Can I create the confusion, then use that confusion as my defense?

MED-PED: An Integrated Genetic Strategy for Preventing Early Deaths

The initial goal of this effort is heterozygous familial hypercholesterolemia (FH). This is one of the most common and best understood serious single gene disorders. Clinical and genetic diagnoses are reliable, relatively inexpensive, and available worldwide. Potent and effective medications are available that act to protect against atherosclerosis.

The methods for diagnosing FH are well developed. In many locations DNA testing is available for accurate diagnosis of locally common mutations. In addition, reliable clinical criteria using inexpensive and widely available blood lipid testing in index cases and relatives have been published showing 98% specificity compared to DNA testing (Williams et al., 1995). Sensitivity for clinically diagnosing FH was 87% in first degree relatives. Different cholesterol cut points have been established to diagnose FH in general population screening and FH family screening. For example, 110 mg/dl is too low for diagnosing FH in the general population (only 2% above 110 have FH), in first degree relatives 95% of those above 110 have FH. This approach recognizes that the probability of FH at a given cholesterol level depends highly on the probability of having FH before testing. The criteria for the diagnosis of FH by age and relationship to a known FH case are given in Table 2.

Right: note the concern for false negatives and the absence of any mention of false positives.
Genotypic or Phenotypic? Which one is more accurate? ... As for profit, why not neither one?

In 2012, Nordestgaard and Benn, and two others, used mostly a clinical scoring system in the 1st Danish report. Genetic hits of the top four most frequent mutations constituted a minority of these FH results. We are supposed to infer that the other mutations, which were not targeted in the genetic testing, are present in the scoring system’s results. But my reconciliation of the Danish reports demonstrates that this is mathematically impossible. (See fhprevalence.com and also pages 28 and 48.) In 2016 the same four authors used only genetic testing, targeting the same four mutations, for their prevalence results, and this time we are supposed to derive, mathematically, the number of remaining mutations. However, we can also compare -- decisively -- these

2016 genetic results to the 2012 genetic results. This is decisive because two-thirds of the same people in the 2012 report are used in the 2016 report. The use of mostly the same population leaves us with an opportunity for a critical deduction. I cannot, for example, say that a slice can be larger than the pie it is cut out of. Just so, the number of genetic hits which originally also passed the scoring system in 2012 cannot possibly be more than the genetic hits which also originally passed the scoring system in 2016. Thus, the majority of genetic hits in 2012 did not originally pass the scoring system, but were promoted after genetic testing. Using the authors own method for mathematical derivation, their counterpart -- the untargeted mutations -- were abandoned in 2012.
Reconciliation of the Danish reports and an examination of the Regeneron report show us the critical failure in the scoring systems. (See fhprevalence.com) If we keep both the scoring systems and the genetic testing available, we lump mostly non-FH in with the FH. FH’s “clinical variability” precludes use of the clinical scoring systems. When we see that there is a pervasive variability of scores in both on-target and off-target populations, we also see that both on-target and off-target share the same scores. Using these scores does not distinguish between these on and off-target populations, we simply hide that fact that we have lumped them all together. The majority of those who pass the scoring systems are mostly non-FH and the majority of those that are genuine FH fail the scoring systems. How did we get here? Through citation kiting, the “art of not defining” FH has succeeded.

Some evidence and knowledge gaps exist in the application of FH genetic testing. Importantly, both phenotype-based and genotype-based definitions of FH should continue to be used, and clinical variability in patient presentation should be acknowledged.

The majority of those who pass the scoring systems are mostly non-FH and the majority of those that are genuine FH fail the scoring systems. How did we get here? Through citation kiting, the “art of not defining” FH has succeeded.
“Shift[ing] the impetus” from Genetic testing to Scoring Systems, and even discouraging Genetic testing.

Dr. Seth Baum was highly paid by Aegerion. Now he is highly paid by Amgen. He proposed an algorithm for identifying FH patients. He is also treasurer for the FH Foundation, a charity funded by big pharma, and this foundation also promotes an algorithm. The word “Algorithm” sounds sophisticated and full of the future. But a common recipe for chocolate chip cookies is an algorithm. Setting this FH scheme to the tune of an “algorithm,” applied to a computer database of patients, only leverages the consequences of the error. Reading the pharma-funded reports, it is at the highest priority to keep the scoring systems front and center and genetic testing at a lower priority ... just barely in there to locate those who would otherwise be left behind. Although identifying the lower scoring, milder FH is of high value, correctly diagnosing the severe non-FH within those FH phenotypic results should not be neglected. This extensive pattern of emphasizing the non-genetic approach to this admittedly genetic disease suggests orchestration and coordination.

The doctor’s dilemma: Challenges in the diagnosis and care of homozygous familial hypercholesterolemia by Seth J. Baum, MD on December 29, 2014

“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 (Fig. 3) [Figure 3 is an elaborate algorithm for identifying FH without genetic testing. Its caption is below.]

But variability precludes use of the scoring systems.

“Shifting the emphasis.”

This is the key to the strategy. It swaps in errors.

“Fig. 3 Novel care pathway for identifying and treating patients with FH. In view of the recently recognized wide genetic and phenotypic variability of FH, this algorithm is intended to simplify and improve care of patients with this disorder. The algorithm shifts the impetus of therapeutic intervention choices from genetics to phenotypic/clinical expression. The individual patient with his or her disease is emphasized.”

https://doi.org/10.1016/j.jacl.2014.12.003

Diagnosis of homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia: Diagnosis may be made on the basis of genetics, clinical criteria (Box 1). While genetic testing may provide a definitive diagnosis of FH, it is recognized that in some patients genetic testing remains elusive, despite exhaustive investigation. Indeed, the existence of additional FH genes cannot be excluded. Historically, FH has been most commonly diagnosed on the basis of an untreated LDL-C plasma concentration >13 mmol/L (>500 mg/dL), or a treated LDL-C concentration of >8 mmol/L (>300 mg/dL), and the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with FH in both parents.

For these reasons, a recent American Heart Association Scientific Statement advocated for a revised diagnostic classification linking proposed International Classification of Diseases, 10th Revision codes, which allow recognition of FH in the bi-data lexicon, to a clinical or phenotypic diagnosis and to genetic diagnosis (Table). Further research will...
Let's look again at the industry’s most influential report. This report is also led by one of the authors of the 1st and 2nd Danish reports. See fhprevalence.com for a reconciliation of these reports. In brief, the scoring systems and genetic testing find mostly different people. An important element of the publication strategy is not to eliminate genetic testing; the reports, funded by the industry, only advocate the demotion of genetic testing, while preserving scoring systems as if they were sufficient and of the highest priority. Once the two methods are no longer regarded as two steps to a single procedure, they can be presented as alternative procedures. The industry will then get the best of both worlds. Critically, the scoring systems are more profitable than genetic testing: first, because it is easier to apply the scoring systems; second, there are more non-FH who will be named FH than otherwise; and third, because most of the genuine FH are actually milder than previously thought, undermining the case for prescriptions but also undermining the marketing message of “danger” and “urgency.”
Two Gold Standards? Where the “old” is genetic matching, and the “new” is epistemologically akin to circumstantial evidence.

The underlying molecular defect of FH consists of mutations in the gene coding for the LDL-receptor protein, detection of which provides the only unequivocal diagnosis. ~ Aalst-Cohen, et al.¹

The importance of establishing the identity of a causative mutation in an index case lies in the certainty that it provides an unequivocal diagnosis in that family, thereby permitting the identification of affected family members at a much younger age and optimizing the health benefit accruing from initiation of treatment as early as possible. ~ Liyanage, et al.²

A molecular diagnosis, i.e. demonstration of a pathogenic mutation in the LDL receptor gene, therefore establishes an unequivocal diagnosis. ~ Fouchier, et al.³

The gold standard of diagnosis is the identification of the underlying genetic defect, which is possible in 80% of cases and enables the identification of affected relatives of the index patient. ~ Klose, et al.⁴

That was before. In the bottom right, we observe 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.

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¹ Diagnosing familial hypercholesterolaemia: the relevance of genetic testing, Emily S. van Aalst-Cohen, et al.
² Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution, Khemanganee E. Liyanage, et al
³ The molecular basis of familial hypercholesterolemia in The Netherlands, Sigrid W. Fouchier, et al.
⁴ Familial Hypercholesterolemia: Developments in Diagnosis and Treatment, Gerald Klose, et al.
1999 Porkka: If we meet the criteria and no FH mutation is found, it might be FCH
Nordestgaard et al’s logic in the 2013 EAS’ authoritative report makes identification of FH consistent with indefinability. Just speaking mathematically, if the FCH outnumber the FH by 5 to 1, then using the characteristics shared between them as “FH identification” we end up with an 80% chance that we have misdiagnosed FCH as FH. This is the classic base rate fallacy that Kahneman and Tversky (page 9) warned us about, and upon which Williams found a mathematical advantage (page 11). Why are the unidentifiable the more precisely defined FH and not the less precisely defined FCH?

Given that the prevalence of FCH is 5 times greater than FH, in the absence of a mutation, and after de-emphasizing TG, FCH is probable at this point. There is not even a mention of the alternative probability: FCH. Once acquainted with FH history, its absence here is conspicuous. Rather than consideration for other diseases, we find the tacit admission that the unclassifiable are presented in euphemism as if there were a “nonclassical” FH. Also, if I refer to a “classical” definition, I imply a newly created definition – but this new definition ... lacks definition.

2013-8 Authoritative Report
doi:10.1093/eurheartj/eht273

The industry’s authoritative report begs the question of FCH, assuming that the genetically unidentifiable are non-classical FH.

It is more like 50% to 80%. See Fhprevalence.com

Conversely, with Porkka, the exclusion of those identifiable by the presence of FH mutations results in a pool of probable FCH.

Even after redefinition by pharma-funded papers, FH is still well-defined by mutations in the LDLR “pathway.” On the other hand, FCH has not yet been “pin-pointed” genetically – even though it is suspected to have a genetic basis (right). If the phrase “other key genes” means beyond the LDLR pathway (above, left) then mentioning this one possibility does not exclude the greater probability that these are FCH. Why isn’t FCH mentioned here?

1997 Porkka
Atherosclerosis 133 (1997) 245–253,

Phenotype expression in familial combined hyperlipidemia

Kimmo V.K. Porkka 1, Ilpo Nuotio 1, Päivi Pajukanta 1, Christian Ehnholm 4, Leena Saarinkorvi 1, Mikko Syvänen 1, Terho Lehtimäki 1, Anne-Taina Lahdenperä 1, Sumi Lahdenperä 1, Kati Yitoku 1, Marijatta Antikainen 1, Markus Perola 1, Olli T. Raitakari 1, Petri Kovanen 1, Jorma S.A. Väärä 1, Leena Peltonen 1, Marja-Riitta Taskinen 1

Key unresolved issues for FCHL are the genes behind this disorder, the extent of genetic (locus) heterogeneity and the mode of inheritance. Further, since the definition of FCHL is based on statistical phenotypic criteria; i.e. fractile cut-points for serum lipids, it is inevitable that a substantial number of phenocopies exist. These factors hamper the genetic and metabolic study of this complex disease. To reveal the pathogenesis of FCHL, studies addressing both the genetic and metabolic aberrations in well-defined pedigrees ascertained through strict diagnostic criteria are needed. Unfortunately, no universally accepted diagnostic criteria exist for FCHL, which makes it difficult to compare the results of different studies.
Fact-ectomy of TG is Modus operandi:

Something happened here and some questions need to be answered. FH is now the target for new drugs, especially the PCSK9 inhibitors. But they were, and still are, also targets for statins, and those have been around for a while now. We can see that the regression from genetic emphasis to the scoring systems begins early.

From MEDPED to DLCN

#1: Genetic testing is listed first, and given the highest priority (left). It will be demoted to last place, even though the presence of the mutation is sufficient, scoring 8 points (center & right).

#2: Establishing a superior “prior probability” before lipid testing (left) is also dropped (center & right). Mention of the advantage of tracing genetically confirmed relatives (left) is removed (center).

From old DLCN to new DLCN (center and right screenshots):

#3: The mentioning of TG as a warning flag for misdiagnosis (center) is also missing by the time we get to a DLCN representation in Austin et al in 2004 (right). This scheme is much more likely to include the FCH than the original MEDPED, both due to upending priorities and to snipping out elements.

#1. Genetic testing is at the top of the list. It will be last.

#2. The mathematical advantage of following up on genetically confirmed relatives is dropped.

#3. Triglycerides are dropped. Abnormal TG suggests FCH.

Williams’ solution to base rate fallacy is missing.
2011 Goldberg, et al, and Triglyceride: a conspicuous reversal

It is unclear to me ... who decided to reduce concern for triglyceride levels when identifying the FH? But it is equally clear that such a reversal took place. A very big push on several fronts occurs in 2011, in a series of papers, with Pharma’s heavy footprint. It includes a blatant de-emphasis of triglyceride. Left, in 1993 Williams et al go to great lengths to warn doctors about possible mix-ups with FCH and FH. Williams presented many distinguishing criteria, and triglyceride is one of them.

When identifying the FH, he tried to “close the door” on the FCH to prevent misdiagnosis. Now in 2011, in Pharma-funded work, instead of presenting high triglyceride as a red flag when diagnosing FH, the door is actually left open to the FCH — with no warning or concern for misdiagnosis. Taking a step up to the inclusion of FCH involved taking a step down from triglyceride emphasis.
2013 Cicero on FCH compared to the 2011 series and 2013 EAS consensus

While it is technically true that high TG does not exclude FH, it is also true that, stopping short of genetic testing, those with high TG and high LDLC, are probably FCH and not FH. I could also hear, with the same technical validity, a game show host telling me, “You may have already won the Publisher’s House Sweepstakes.”

Those with Familial combined hyperlipidemia (FCH) tend to have a combination of high TG and high LDLC. On the other hand, the FH tend to have high LDLC but relatively normal TG. So high TG is what typically separates the FCH from the FH.

Should I waste my time on the highly improbable yet still technically and merely possible? TG is the “lynchpin” to several causes of dyslipidemia, but especially FCH. By removing this concern for TG levels, one “leaves the door open” for the FCH to wander in.

So if I truly want FH, but do not test for the mutation itself, then I must exclude those with higher-scoring TG levels. But if I want to include the FCH in my FH result, I neglect or at least de-emphasize the issue of higher TG.

“Unremarkable” is ambiguous. It should mean, “normal.” But the sentence that follows says that elevated TG “does not exclude the FH diagnosis.” Taking the two phrases together, “unremarkable” is open to the meaning, ‘we shouldn’t pay too much attention to TG.’ The authors have the reader aim for the less probable FH in the place where the more probable FCH abound. We read, “Don’t think too much; you can still push the green button if you find high TG,” where we should read, “Push the red button and think things over if you find high TG.”
Raking Leaves into the pile that you need: After de-emphasizing genetic testing and exclusionary criteria, FCH Pass as FH

1997 Ascaso vs 2013 Nordestgaard: After removal of TG top-scoring FCH become FH

De-emphasizing genetic testing and eliminating TG levels keeps the FCH blended in with the FH. Without appropriate exclusionary criteria, both the on-target and the off-target populations maintain a pervasive variability of scores, and the patient swap is now a fait accompli. The chart on the left is the industry recommended scoring system for FH. Genetic testing is demoted and optional, and there is no mention that a negative genetic test should serve as a red flag for FCH. Also, finding one family member with cardiac disease is a characteristic shared with FCH and is not as exclusionary as a serious examination of an extensive family pedigree. **Base rate fallacy is present here.** On the right is a presentation of Ascaso et al’s FCH cohort. It can be seen that scores consistent with FH are present. Unexamined, the FCH with an FH score are “FH.” For later analysis, note that these FCH (right) weigh in at the second level of the FH scoring system (left), aggregating at the Probable category, 6 to 8 points.

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**Table 1** Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolaemia in adults

<table>
<thead>
<tr>
<th>Group 1: family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) First-degree relative with known premature (55 years, men; 60 years, women) coronary heart disease (CHD) OR</td>
</tr>
<tr>
<td>(ii) First-degree relative with known LDL cholesterol &gt;95th percentile by age and gender for country</td>
</tr>
<tr>
<td>(iii) First-degree relative with known LDL cholesterol &gt;95th percentile by age and gender for country</td>
</tr>
<tr>
<td>(iv) Child/ren &lt;18 years old with known LDL cholesterol &gt;95th percentile by age and gender for country</td>
</tr>
<tr>
<td>Group 2: clinical history</td>
</tr>
<tr>
<td>(i) Subject has premature (55 years, men; 60 years, women) CHD</td>
</tr>
<tr>
<td>(ii) Subject has premature (55 years, men; 60 years, women) CHD</td>
</tr>
<tr>
<td>Group 3: physical examination</td>
</tr>
<tr>
<td>(i) Tendon xanthoma</td>
</tr>
<tr>
<td>(ii) Coronary atherosclerosis in a person &lt;45 years</td>
</tr>
<tr>
<td>Group 4: biochemical results (LDL-C, HDL-C, triglycerides, VLDL-C)</td>
</tr>
<tr>
<td>(i) LDL-C &gt;5 mmol/L (&gt;200 mg/dL)</td>
</tr>
<tr>
<td>(ii) LDL-C &gt;5 mmol/L (&gt;200 mg/dL)</td>
</tr>
<tr>
<td>(iii) LDL-C &gt;5 mmol/L (&gt;200 mg/dL)</td>
</tr>
<tr>
<td>(iv) LDL-C &gt;5 mmol/L (&gt;200 mg/dL)</td>
</tr>
<tr>
<td>Group 5: molecular genetic testing (DNA analysis)</td>
</tr>
<tr>
<td>(i) Mutation in the LDLR, APOE, or PCSK9 genes</td>
</tr>
</tbody>
</table>


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**Table 1** General characteristics of the study subjects

<table>
<thead>
<tr>
<th>FCH group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67 (46, 22, 85)</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.1 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 ± 2.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142.0 ± 11.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>86.2 ± 13.0</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>7.56 ± 2.7</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>3.17 ± 1.0</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>5.00 ± 0.49</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.09 ± 0.29</td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>1.40 ± 0.17</td>
</tr>
</tbody>
</table>

**Criteria for FCH (right) requires family history of premature CVD,**

1 point **on the FH checklist** (left).

**11 with premature heart disease in the FCH group (right), 2 points on the FH checklist** (left).

The average FHC patient in this cohort was over 5 LDL-C, scoring 3 points **on the FH checklist.**

Thus, FCH can easily score 6 and be diagnosed as “Probable FH.”

**The red flag of TG levels has been removed.**

**How many FCH on the right pass as FH according to the recommended criteria on the left? Without responsible exclusionary criteria the FCH will be blended in with the FH.**
1999 Aouizerat vs. Nordestgaard

On the left we see the industry’s engineered scoring system for FH; on the right, a scoring system for FCH. The enabler is the fact that although FH has been precisely defined at the genetic level, the exact cause of FCH is still up in the air. So removing emphasis on genetic definition and removing the criteria which distinguishes the FCH from the FH – Triglyceride levels – blends the FCH with the FH.
2014 Skoumas vs 2011 Goldberg: The FCH score as FH if not precluded by TG

Here we will juxtapose characteristics consistent with both FCH and FH to illustrate the overlap between the two diseases when high TG is not stressed as a red flag within the FH scoring system. High LDLC dominates the FH scoring system, and it is also a characteristic shared with FCH. Higher scoring FCH, if there is no consideration for TG levels, will inflate the FH count. On the left in Skoumas et al, the average LDLC level for FCH was 209 mg/dl. On the right, Goldberg et al’s report recommended an LDLC cutoff point of 190 mg/dl. A family history of early heart disease is also a part of both diagnostic systems. Prevalence for the FCH is five times greater than that of FH (page 18). Without a concern for TG levels, if a patient is first diagnosed as FH and is later subjected to a genetic test, it is highly likely, given base rate analysis, that the patient is probably FCH and will not have an LDLR mutation. (See proof of this in my reconciliation of the Danish reports: fhprevalence.com.) With the industry’s funded research, we do not even get a red flag. One neighbor, Mr. Brown, has an oak tree and the other neighbor, Mr. Smith, has a maple tree. Each pays Tom Sawyer to rake up the leaves. How much Tom gets paid depends upon the height of the pile. So Tom rakes up both sets of leaves, raking Mr. Smith’s just over Mr. Brown’s boundary. Tom shows Mr. Brown and asks him to pay. Then Tom rakes all of the leaves from that pile back over Mr. Smith’s boundary and shows Mr. Smith, collecting payment. Likewise, the same patients can be FCH now and FH later, as we care now and don’t care later about TG levels and genetic testing.
The 1st and 2nd Danish reports rake in different patients, with different TG levels

Raking leaves into the pile that you need, when you need it. The Copenhagen General Population Survey (CPGS) was founded by Nordestgaard and Tybjaerg-Hansen, authors on the 1st and 2nd Danish reports. They are also on the 2013 EAS report, the industry’s most influential FH statement. The CPGS performed genetic testing on randomly selected individuals, but only for the three most frequent LDLR mutations and the R3500Q APOB mutation. Basically, the authors of the 2012 and 2016 reports assembled results from a study which used the same procedure, on mostly the same people. However, for the 2012 report, a circumstantial scoring system was used to pull from those results a pile of “FH” patients, with genetic hits simply being added in. At this time there were 69,000 people in the study. By the time we get to the 2016 report, there will be almost 100,000. This means that about 2/3rds of those used in the 2012 report are also used in the 2016 report. The same four authors from the 2012 report write the report in 2016. The 2013 EAS report, including three of the above four authors, claims this 2012 Danish report as its source for prevalence. The results from the 2nd report presented (below right) rely solely on genetic testing. The two resulting prevalence numbers were said to “compare” with each other. They do not. Only the quantities are similar. My deductive reconciliation of the two reports (see fhprevalence.com) proved without a doubt that the two quantities represent mostly different people – yet both were called FH. Reconciling the two Danish reports, the evidence is strong that out of the same raw data, the FCH and other non-FH are raked up into an “FH” pile in 2012, and then through the genetic approach, a different “FH” pile is raked up in the 2016 report. It is however mathematically impossible for the majority of those in these two piles to be the same people. They are mostly different people. The grossly divergent TG levels in the 2012 and 2016 reports leave this fracture conspicuous. FH is noted for having relatively normal TG levels. On the other hand, FCH is noted for high TG levels. On the right, the 2016 result is solely from genetic testing, and average TG levels are close to the general population, about 1 mmol/L. On the left, the 2012 results are mostly from the scoring system, which does not exclude for TG and which includes passing scores regardless of mutation status, and where we can plainly see that the TG level is nearly twice as high as that found in the 2016 genetic results. The higher TG in the 2012 report is consistent with FCH and non-FH.

2012 1st Danish Report
Most passing scores are without regard for mutation status.

2016 2nd Danish Report
Mutation carriers regardless of scores.

Both studies are by the same authors, using mostly the same population. But the 1st report relies mostly on the scoring system and the 2nd report, on DNA testing.
A Bulge in the Statistics and an error at precisely the point where we would distinguish the FH from the FCH

Barring a genetic test, TG is what distinguishes FCH from FH. Out of six charts in the 2016 2nd Danish report (below, right), the chart for TG is the only chart with an incorrect label (“1.7”). The broken lines (below, right) are supposed to represent the level of the general population, and we can see that TG is about 0.9, where the broken line sits at the left margin of the 2nd Danish report. But the erroneous printing of “1.7” at the right margin can lead a quick reader to compare it to the 1st Danish report’s result, “1.9.” The FH tend to be closer to normal TG on average whereas the FCH tend to have elevated TG. Also, the 1st Danish report can serve as a proxy for the recommended diagnostic system: a system that weighs circumstantial evidence and provides a score. Higher TG in the 2012 report is consistent with misdiagnosis of the FCH as FH. On the right, in the 2016 report, we see solely molecular results which are consistent with the lipid profile of FH: TG are much lower and closer to normal. The same mutation types on the right, at about 1 mmol/L TG, are accounted for within the TG number in the 2012 report; however, those without a mutation status yet with passing scores have been added in – a majority. So to get an average of 1.9 in the 1st Danish report, there must be a different set of people making up this 1st Danish report, and that group added in must be even higher than 1.9. We remember that both reports share mostly the same population. Thus, it is clear: when counting only genetic results TG levels are normal, and when including passing scores regardless of mutation status, TG levels double. The doubled TG is consistent with adding in the FCH, and other non-FH, into the FH population. This is achieved in part by de-emphasizing the genetic basis for FH, but also by removing regard for high TG levels in FH identification instructions.
Bulge in the Statistics: Accepting those with High TG includes those with METS and T2DM. 2016 EAS returns to outline the distinguishing points of FCH, exposing a statistical “bulge” in the new version of “FH,” a bulge consistent with the presence of non-FH. FCH characteristics overlap with type 2 diabetes and metabolic syndrome. These non-FH have typically higher TG levels.

When the same authors list FH criteria in this same 2016 report, TG is conspicuously absent. (To review Goldstein et al, see pages 7 and 8; and for Williams et al, pages 11 and 12.)
2008 Civeira et al and the predictable bulge in later statistics

Damgaard’s study (doi:10.1016/j.atherosclerosis.2004.12.001) shows us that the Dutch scoring system used in the 2013 EAS report is consistent with a 50% hit rate. In the other 50% no mutation was found. The Definite FH will have a greater presence of verified mutation carriers (~2/3) than will the Probable FH (~1/3). Van der Graaf went on to show that this was due to inadequate exclusionary criteria (See pages 16 and 17). If both FCH and FH can have passing scores as “FH” and if FH has relatively higher levels of LDLC scoring at Definite FH, while the FCH aggregate at the next lower category -- Probable FH -- with relatively higher rates of obesity, diabetes, and metabolic syndrome, then one would expect to see a spike of rates of obesity, diabetes, and metabolic syndrome in that next lower category and in inverse proportion to the severity of the FH score. And that is precisely what we see here. Having no exclusion for TG in the 1st Danish report, all other diseases with high TG inflate the “FH” results: T2DM, Obesity, and METS for example. And FCH can be associated with all three. On the right, we have Civeira et al. Patients were originally diagnosed as FCH, but then tested for FH mutations. Those who were actually FH, compared to the remaining FCH, had higher LDLC but lower rates of T2DM and Obesity. At bottom left, we see Benn et al in the 2012 1st Danish report. Patients were deemed to have FH by a scoring system where LDLC levels dominate. Those with lower scores, and thus, tending to have lower LDLC had higher rates of Diabetes and Obesity. Also, by the criteria of the Dutch scoring system, the Definite FH will tend to have higher LDLC than the Probable FH. But note that obesity and T2DM rates are lower for the severest scoring Definite FH but higher for the relatively milder Probable FH. The relationship between FH Definite and FH Probable in the Danish source for the 2013 EAS authoritative report resembles the relationship between FH and FCH.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FH Definite</th>
<th>FH Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>130</td>
<td>37</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.30</td>
<td>0.23</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58 (46-69)</td>
<td>51 (52-66)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (22.9-29.7)</td>
<td>25.7 (24.9-30.5)</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>30%</td>
<td>63%</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>97</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension, all (%)</td>
<td>32</td>
<td>70</td>
</tr>
<tr>
<td>Hypertension, non-diabetes (%)</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>32</td>
<td>68</td>
</tr>
<tr>
<td>Heart disease, non-mitral valve (%)</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>Heart disease, mitral valve (%)</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>Heart disease, mitral valve (%)</td>
<td>30</td>
<td>67</td>
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<td>Heart disease, mitral valve (%)</td>
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</tr>
<tr>
<td>Heart disease, mitral valve (%)</td>
<td>30</td>
<td>67</td>
</tr>
</tbody>
</table>

**Table Note:** Those patients diagnosed as FH and in whom no FH mutation was found had higher TG than those misdiagnosed as FCH but who were really FH (i.e., those in whom an FH mutation was found).
Type 2 Diabetes is greater in FCH than in FH

As we’ve seen, obesity and metabolic syndrome are associated with FCH more than with FH, and we saw a bulge in the statistics precisely where the chance of misdiagnosis is greater, in the Probable category (See previous page). However, the presence of type 2 diabetes mellitus (T2DM) is especially telling. T2DM is actually inversely present in FH in contrast with the FCH. That is, it is not merely a matter of degree, but the tendencies of T2DM in FCH and FH are in opposite directions. Surprisingly, the FH tend to have lower than normal rates of T2DM. Here are some facts about FH, FCH, and T2DM. Next, we’ll look at the T2DM “bulge.”
T2DM: The Bulge from FCH shows up in FH statistics in the Probable category

The 1st Danish report result accepted the four most frequent mutation carriers. These carriers however made up the lesser part of this study’s result. Most were deemed “FH” solely due to passing scores and regardless of mutation status (below left), whereas the 2nd Danish report result (below right) is made up of solely verified mutation carriers. If both FCH and FH have passing scores as “FH” and if FH has relatively higher levels of LDLC, while FCH has relatively higher rates of obesity, T2DM, and METS, then one would expect to see a spike of rates of obesity, diabetes, and metabolic syndrome in the Probable category ... in inverse proportion to the severity of the FH score. And that is precisely what we see here in the 1st Report. T2DM is especially striking, given recent evidence of lower than average prevalence among the FH. FH LDLR mutation carriers have lower rates of diabetes. (It is even hypothesized that carriers are protected against diabetes.) Not so for the FCH, they are prone to diabetes. Consistently, the mutation hits in the 2nd Danish report have much lower presence of diabetes than the passing scores in the 1st Danish report. This is consistent with the fact that the FCH can pass the scoring systems (left), if a responsible process of exclusion is not present. Note that the diabetes rate in the recommended scoring system (left) is twice that of the diabetes rate of the mutation carriers alone (right).

Lower standards for the Probable score result in lower accuracy when compared to the higher standards and higher accuracy with the Definite score. Consequently one would expect more misdiagnosis with the Probable than the Definite. Also, the FCH tend to have relatively lower LDLC than the FH, so they will aggregate below the mass of higher scoring FH. Add to this the fact that the FCH have higher rates of diabetes than the FH do. This resulting bulge in T2DM below is consistent with misdiagnosed FCH in the Probable FH category.

In short, APOB carriers tend to have higher rates of diabetes than LDLR carriers, but the FCH have even higher rates. The results from the scoring system on the left shows a much higher diabetes percentage than does the purely genetic results on the right. Both Danish reports involve the same authors and 2/3rds of the same population. Diabetes percentages do not correspond. I have already proven elsewhere, deductively, that these two FH studies identify mostly different people, despite the authors’ claims of comparability with their results. Here as well, the evidence shows two different groups of people: the FCH probably account for the much higher rate of diabetes in the scoring system’s “Probable FH” category in the 1st Danish report (left table). It has almost twice the percentage of T2DM as the results from molecular testing in the 2nd report (right table).

1st Danish report
doi:10.1210/jc.2012-1563

2nd Danish report supplement
doi:10.1093/eurheartj/ehw028

Supplementary Table 3. Participants in the Copenhagen General Population Study by carrier status of low-density lipoprotein receptor (LDLR) and apolipoprotein B gene (APOB) mutations.
Review of strategy through latest addition to the FH diseases

Nordestgaard was the lead author of the 2013 EAS report. He is also an author on both the 1st and 2nd Danish reports. Nordestgaard put together a series of slides for the FH Foundation’s 2015 gathering. Some of the same slides are available in PDF form on the internet. The FH Foundation was and still is heavily funded by the pharmaceutical industry -- Aegerion (in the past), Amgen, and Regeneron, for example. In Nordestgaard’s earlier work, the APOB and PCSK9 mutations were blended in with the LDL-Receptor mutations, and all three were called “FH” -- ostensibly because, although the other two are not receptors, per se, they are associated with the “receptor pathway.” But now three of the four authors from the Danish reports – Nordestgaard, Benn, and Tybjaerg-Hansen – co-author a new report that includes another disease as FH which is not even associated with the receptor pathway: Lp(a).

How does Lp(a) tell us not to bother with genetic testing for FH yet to name them “FH?”

1. Above: FH was originally defined by the presence of an LDL-Receptor mutation.
2. Above: As I’ve demonstrated earlier, since Goldberg et al’s 2011 series, other mutations are stripped of their own names and are subsumed under the name “FH,” ostensibly because they are in the receptor-pathway.
3. Left: Now, through Langsted and Nordestgaard, Lp(a) is rolled up within the name “FH,” even though Nordestgaard also tells us that Lp(a) is not affected by the receptor-pathway.
2018: LP(a) a new target of citation kiting, which fits the pattern: the FCH are thereafter assumed to be FH

This example of citation kiting, along with the others, leaves us with more evidence that FCH is a target for “FH” sales. What is cited as “phenotypic FH” in Sturm et al (left) is clearly FCH in the source, Ellis et al (top, right). And in Sturm (left) there is no mention of FCH … at all … even though their citation clearly calls for it: the title of the source material itself tells us that FCH can mimic FH. Also note that originally “FH” was defined by the presence of the LDLR mutation. Then due to citation kiting from 2011 on, “FH” included other non-receptor mutations because they were in the receptor “pathway,” i.e., the APOB and PCSK9. Now lipoprotein(a) is not even associated with the receptor pathway and yet is here said to be a “possible cause of clinical familial hypercholesterolemia.” Many of the authors receive pharma money. This is another example of using citation kiting to bring other diseases within the range of “FH” drug sales, and again fitting the pattern that profits Big Pharma: citation kiting results in the assumption that the FCH are FH.
From MEDPED to DLCN: Nordestgaard

**1996 MEDPED Williams et al. DOI: 10.1007/978-3-642-61028-8_5**

DNA mentioned first.

**2013 EAS: the Pharma-funded authoritative report, Nordestgaard et al. doi:10.1093/eurheartj/ehs273**

AND versus OR.

TG is exclusionary step, left: No such exclusionary step in the "expert" recommendation, right.

In addition to a family relative as an isolated characteristic (d), make a pedigree investigation of bimodal expression (e).

“Prior Probability”/“Base Rate” strategy allows us to both lower the LDL threshold and improve accuracy at the same time.

DNA mentioned last.
Dr. Seth Baum and marketing for Big Pharma.

“People are literally dying waiting for these drugs. That is not hyperbole. They are literally dying online waiting for the drug. So that has to come to an end.” ~ Dr. Seth Baum, video interview. He received payments from Amgen, Aegerion, and others. ~ AJMC, Apr 2017
https://www.youtube.com/watch?v=2zzbV6rXikA
The similarities in clinical profiles between accepted and rejected patients suggest concerning inconsistencies in the approval-rejection process," said Seth Baum, M.D., president of the American Society for Preventive Cardiology and lead study investigator. ~ PR, THOUSAND OAKS, Calif., March 19, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN)

My analysis refutes the Science-as-PR which has been re-published as news in the WSJ. The manipulation of the diagnostic procedure begins with a 2011 series of reports. Aegerion was involved in its funding. Dr Baum was peer reviewer of this journal at that time. He currently promotes this misinformation. The number of prescriptions being denied is consistent with the misdiagnosis consequent of an equivocation strategy. Taking advantage of isolated characteristics shared between different diseases is the end result of Baum’s language strategy. Consequently, prescriptions are not rejected “despite” the fact that denied and approved patients share the same characteristics; they are denied because different diseases can and do merely share isolated characteristics.

Wiley: Clinical Cardiology
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RESEARCH

PCSK9 inhibitor access barriers — issues and recommendations: Improving the access process for patients, clinicians and payers

Seth J. Baum1 | Peter P. Toth1 | James A. Underberg1 | Paul Jellinger2 | Joyce Ross3 | Katherine Wilenm1

FH Foundation, funding from Amgen, Regeneron, and others.

$367,000 received from pharma between ‘13 ~ ‘16

$891,000 received from pharma between ‘13 ~ ‘16

$325,000 received from pharma between ‘13 ~ ‘16

$1.23 Million received from pharma between ‘13 ~ ‘16

This is a marketing effort, designed to get past red tape. There is no scientific issue here.
Through a series of “fact-ectomies” performed on the historical record, the definition and identification procedures of FH have been equivocated.

Editorial

The doctor’s dilemma: Challenges in the diagnosis and care of homozygous familial hypercholesterolemia

by Seth J. Baum, MD on December 29, 2014

In this 2014 document, Dr. Baum actually outlines an equivocation strategy.

“Evolution of a definition”

“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.”

More people are not found, the historical definition is changed: other disease names are rolled up within the name, “FH.” The only “evidence” supporting 1/160,000 is that of linguistic manipulation, carried out by way of “citation kiting.”

“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.”

Not education … but re-education.

“Reeducation is in order; teaching medical practitioners to have FH as a fixture on their differential diagnostic list of LDL disorders is crucial.”

From the beginning, confusing the FCH with the FH was a big part of the strategy. By removing a mathematical advantage employed in the original MEDPED strategy, disregarding genetics, and eliminating concern for high triglyceride levels, most “clinically severe FH” today are not really FH. They suffer from other diseases.

“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.”
We don’t reject these *despite* the fact that they share the same characteristics with FH. We reject them *because* they *merely* share the same characteristics with FH.

If I relax the TG threshold and let it drift *upward*, then more FCH, METS, T2DM, and Obese will be considered “FH.” *If TG is not even considered, higher LDLC scoring FCH and other Non-FH can pass the FH diagnosis.*

Replacing 1st *degree relatives* of a known carrier with a *single family member who has a history of heart problems* also replaces the *leveraged prior probability* with an *isolated characteristic shared with the non-FH*, the latter of which now *employs* the very Base Rate Fallacy that the former had overcome. Doing so swaps out the lower scoring FH, swapping in the higher scoring FCH, METS, T2DM, and the obese.

Without DNA testing or a sufficient family pedigree analysis *and following through with Cascade screening* these will be abandoned — a *majority of the FH.*

If I lower the cutoff score to bring in more lower-scoring FH, I bring an even greater proportion of Non-FH into the “FH” results. If there is no serious *exclusionary* step, these are effectively renamed, “FH.”