

Precision Medicine— Too Much Precision, Not Enough Medicine?

by David W. Moskowitz

“Precision medicine,” a new name for “molecular medicine,” has been the goal of medicine since the time of the Greeks. Medicine without scientific precision is quackery.

The problem is that human biology and disease are far too complex to ever be described with total precision. The same is true for that most precise of the sciences, physics. I doubt that we will ever completely understand the real world. Only God is supposed to be able to do that. Human knowledge is fractal: the more you know about any subject, the more questions arise. That’s why the best scientists are humble and open-minded, eager to consider new ideas from colleagues. Biomedical science has imitated physics and become Big Science, with a few ambitious pediatric geneticists and Mendelian linkage analysts telling everybody else what to do. No wonder Precision Medicine has been off on the wrong foot since the 1980s.

True, the precision can be impressive—down to a single nucleotide (genomics, transcriptomics); a single methyl group (epigenomics); a single protein (proteomics) or phosphorylated amino acid (phosphoproteomics); a single lipid species (lipidomics) or metabolite (metabolomics); a single commensal bacterial species (microbiomics); or realms yet to be explored, like the “oscillomics” of cellular and subcellular calcium transients, mitochondrial rates of ATP production; patterns of neuronal firing, etc., etc.

But scientific precision without clinical significance is just another false step in medicine’s long quest for the Golden Fleece: knowing how to reproducibly stop a disease. Congressman Dingell used to mock irrelevant science with his famous Golden Fleece awards. I believe that the current pursuit of precision medicine is largely, in Dingell’s memorable phrase, a Golden Fleece.

If Mendelian Diseases Haven’t Been Solved Clinically Yet, Why Are Mendelian Geneticists in Charge?

When Linus Pauling and his colleagues published the amino acid mutation responsible for sickle cell disease in 1949, Glu6Val, they called it the dawn of molecular medicine. Over 65 years later, the only definitive treatment for sickle cell disease is a bone marrow transplant, which is too expensive and dangerous to even remotely qualify as a public health success. Hydroxyurea helps. Blood transfusions are still being studied after decades of grants. Patients still suffer.

Society takes great pride in knowing the precise cause of sickle cell disease—it’s taught in every undergraduate biochemistry course. But we seem to have forgotten that the only goal of biomedical research is to improve patient outcomes.

Mendelian, single-gene disorders are characterized by loss-of-function mutations in important proteins like beta-hemoglobin, the chloride transporter (CFTR) of cystic fibrosis, huntingtin, and dystrophin. The more important the gene, the earlier the onset of disease. So most Mendelian diseases are pediatric. Adult diseases, which represent the major burden of disease in society, are acknowledged to be polygenic.

Most drugs are inhibitors: it's far easier to inhibit a protein than to activate it. If the causative gene is undruggable, as is the case for all Mendelian diseases, the next logical step is to find modifier genes. The list of drug targets must be extended if the top candidate refuses a solution. Most people practice this in other aspects of their life, such as dating. This approach can often do the trick clinically (1-3).

Why haven't pediatric geneticists looked for modifier genes? Perhaps because they don't know how to find them. Linkage analysis doesn't work for multiple loci, each with a small effect. Geneticists use neutral markers spaced along the genome to narrow down the region where a major causative locus resides. This requires linkage disequilibrium between the neutral markers and the causative locus. They have to be close enough to be inherited together, and for recombination not to split them up.

There's plenty of linkage disequilibrium in families, where entire blocks of DNA are inherited intact. But outbred patients have nothing in common except their disease alleles. This is a strength, as we'll see next, but a huge problem for genetic statisticians: there's no linkage disequilibrium in polygenic diseases when outbred patients are studied (Fig 1).

In fact, it's easy to solve polygenic diseases. The mathematics is far easier than the complex linkage analysis of Mendelian genetics. Nothing more complicated than a 2 by 2 table and calculation of an odds ratio (ad/bc) is involved, as Neil Risch suggested (4). One problem is how to correct for multiple comparisons and avoid false positive results. Another is using the wrong SNPs; only functional SNPs work, not neutral marker SNPs. Both problems have led to a 30-year drought in solving polygenic diseases, despite billions of dollars spent on sample collection and genotyping.

Because of their simplicity, association studies flourished in the 1980s and early 1990s, with prestigious journals like Nature and Lancet headlining discoveries for complex phenotypes like schizophrenia. But like all genomic studies, these findings were hard to replicate in other patient populations. (Not using enough cases, i.e. a type I error, is a simple way to "disprove" an association [5]).

Rather than address the underlying biological complexity at the root of the problem—the difficulty in categorizing phenotypes, unknown modifier loci, variability of allele frequencies due to underlying population structure—genetic statisticians insisted on brutal Bonferroni-like corrections, which made most associations disappear. For a decade, the NEJM published expensive but clinically useless genome-wide association studies (GWAS) for cardiovascular diseases (6). Biomedical scientists are proud of the statistical purity of this work, and authors of these studies continued to give and receive NIH funding, but how does it help the poor patient, for whom the whole enterprise is supposed to work?

It's instructive that even genetic statisticians learned to loosen the rules of genetic statistics. To find a dozen genes for type 1 diabetes, for example, John Todd and colleagues had to use a two-stage approach, which was not allowed in classic linkage analysis. The first stage ignored the Bonferroni-like correction. Only the second stage used the more rigorous approach to obtain a LOD score. Interestingly, Todd acknowledged that all of the genes they'd

NOTCH4 (a tumor suppressor in the Wnt pathway)

SNP	Chr.6 location	SNP type	aa residue
1. rs8192579	BP 32,196,022	synonymous coding	Q1809
2. rs8192576	BP 32,197,523	synonymous coding	L1610
3. rs3134942	BP 32,200,994	synonymous coding	V1384
4. rs204987	BP 32,201,155	synonymous coding	T1367
5. rs8192573	BP 32,201,219	nonsyn. coding	R>P1346
6. rs8192574	BP 32,201,368	synonymous coding	S1296

Preliminary odds ratios are given below for the following cancers in whites. The extraordinary SNP rs8192573, converting an Arg to a structure-destroying Pro, is highlighted in bold:

SNP	Breast	Colon	Lung	Ovarian	Pancreatic	Prostate
Q1809	G, 2.0	A, 1.5	G, 8.3	G, 2.0	G,11	G, 2.0
L1610	G, 6.2	G, 6.2	1	G, 6.2	G,13	1
V1384	G, 2.9	G, 2.9	G,11	G, 1.8	G,11	G 2.9
T1367	T, 1	T, 1	A, 7.5	T, 1	T, 1	T, 1
R1345P	C,21	C, 6.2	C,26	C, 6.2	C,13	G,11
S1296	G, 3.9	G, 8.9	G 8.9	G, 7.4	G, 7.4	G, 8.9

found had previously been found using association studies.

Furthermore, linkage analysis is not so precise after all. It involves a fudge factor, called theta, which is the population allele frequency. It is never truly knowable, and must be guessed at before the LOD score can be calculated.

Association studies can be clinically powerful though statistically underwhelming. A high odds ratio ought to be correlated with how rate-limiting that gene is for the disease process. But even an odds ratio of 1, as we found with the ACE D/D genotype in ASPVD (7), can still be clinically significant (8). Indeed, the only way to test whether a variant contributes to a disease pathway is to inhibit the gene that it's in and see what happens to the patient. If a disease can be reversed with a single agent despite a low odds ratio for the genomic variant, then the gene involved must occur very early in the disease pathway.

Indeed, why expect statistically significant odds ratios if thousands of loci are involved? On average, each of a thousand contributing loci should contribute only 0.1% towards the disease. Its odds ratio should only be 1.001, indistinguishable from 1.

Improving patient outcomes should be our goal, not some arbitrary notion of statistical rigor. Recalling this should make Precision Medicine's next decade more productive than its past 65 years. Like any biomedical research result, association studies must eventually be validated clinically. Does the association improve prediction, diagnosis and/or treatment of the patient?

Cancer genomics: tumor vs. somatic DNA

There is so much amplification at each step in a biological pathway that the only hope for delaying, let alone arresting, disease lies in inhibiting early steps. Somatic DNA contains the earliest steps for virtually all diseases. All the other 'omics operate downstream, including tumor genomics. Gene expression and mutations in tumor DNA occur many years after disease begins in the "germline" (really, "somatic") DNA (9).

Using a set of SNPs meant to be functional, we found a large number of tumorigenesis genes. Besides the "usual suspects," e.g. in the Wnt pathway (see Tables), we found many other cancer-associated genes, including olfactory receptors. The large number of genes, perhaps 1/3 to 1/2 of the genome, suggests that solid cancers arise when tissue stem cells fail to differentiate as efficiently as they did during embryonic life. Embryonic tissue has a marked advantage over the adult: an elaborate gridwork of transcription factors to guide differentiation. In the adult, the proliferating tissue stem cell is almost entirely on its own. Since it affects 1 in 3 adults, cancer appears to be a physiologic response to tissue atrophy.

Is it time to abandon model systems?

The ACE insertion/deletion polymorphism exists only in humans, not rodents, roundworms, or fruitflies. Even where model systems have similar components as humans, like the immune system, they may have different set-points. For example, viral lethality appears to be due to the aggressiveness of the host's innate immune response, not to the virus itself. Patients who die from a virus tend to overdo their innate immune response, perishing in a "cytokine storm." Angiotensin II is an early cytokine; all immune cells have AT₁ and AT₂ receptors.

One would therefore expect that blocking white cell activation at AT₁ receptors, while allowing pro-apoptotic signaling through AT₂ receptors, might be a general viral antidote. (It shouldn't work for viruses which induce a state of immunosuppression, like the herpesviridae).

In a small consecutive case series, we found this to be the case. Losartan, an angiotensin II receptor blocker (ARB), helped in 21 of 30 patients (70%) with West Nile virus encephalitis, although the degree of improvement depended entirely on when during the disease it was administered. A patient given losartan in the ER for coma regained consciousness after 12 hr, rather than the usual 72 hr later (see Table 2 in ref. 3). Patients treated several weeks after they had become paralyzed experienced painfully slow recovery, albeit more than expected.

Other species responded differently. Horses with WNV responded poorly to 1000 mg/d losartan (6 out of 12 horses survived, with no quick recoveries). Birds responded variably.

Raptors (great horned owls, hawks, a bald eagle) did well, showing dramatic improvement within the first 24 hr after 1 mg/lb losartan, but corvids (crows) still died within a few hours of presentation.

CTNNA2 (alpha-2-catenin is a tumor suppressor in the Wnt pathway)

SNP	Chr.2 location	SNP type
1. rs4146025	BP 79,650,069	intronic
2. rs3739139	BP 79,651,538	intronic

SNP	Breast	Colon	Lung	Ovarian	Pancreatic	Prostate
rs4146025	A,6.7	A,4.3	A,5.2	A,4.3	A,8.3	A,2.0
rs3739139	C,6.1	C,6.1	C,9.9	C,6.1	C,7.7	C,6.1

The minor alleles of both SNPs are cancer associated. Since CTNNA2 is known to be a tumor suppressor, these alleles are expected to somehow lead to decreased gene expression, although how introns affect gene expression is not yet understood.

In an avian influenza model, losartan had no effect on mortality in chicks, nor did it alter mortality in a mouse influenza model. Humans should now be the study animal of choice. Model systems are largely a waste of time, producing what could either be false positive or false negative results. The most ethical approach to Precision Medicine is thus to repurpose already existing drugs before trying any new agents. If the candidate gene already has a commercially available drug inhibitor with many patient-years' worth of safety data, as is true for ACE inhibitors and ARBs, then safety is not an issue, and efficacy can be tested without delay or expense. This

is ideal, since patients have no time, and researchers nowadays have no money. Medicine is back in the 1930s, with plenty of clinical questions, but no money to study them.

Unlike the 1930s, healthcare has become profoundly anti-innovative. Perhaps global competition on outcomes will help transform even the First World's hospital-based system. Precision Medicine, by enabling preventive molecular medicine, a phrase I coined in 1996, will drastically cut healthcare costs by keeping patients healthy and out of the hospital. Countries without much in the way of healthcare infrastructure—developing countries without hospitals, dialysis units, and research institutes—could actually leapfrog ahead of the developed world in terms of patient outcomes. India and China are more likely to embrace clinically meaningful Precision Medicine, with their hundreds of millions of patients, than the US or the UK.

The idiocy of the community standard

In medical practice nowadays, a physician is not allowed to deviate from the so-called "community standard" of practice. This phrase comes from malpractice law. As long as one is practicing the "community standard," no matter how awful the clinical outcomes, a physician cannot be convicted of malpractice. Administrators have seized on this immunity to insist that every physician adhere to the community standard.

The community standard is easy to establish. Ever since pharmacies became computerized, it's been easy to tell how each physician prescribes. Do they use lots of narcotics for their patients? (In Florida, the use of narcotics

has been virtually criminalized by an ambitious Attorney General). Do they use a higher dose of a drug than everybody else? Reversal of diabetic and hypertensive nephropathy requires 4-5 times the conventional dose of quinapril (8).

Whether the new practice is safe doesn't matter; high-dose quinapril, for example, is quite safe (8). Any hyperkalemia can be easily controlled with fludrocortisone (8). The legal argument is that if anything bad happens while the patient is on the higher dose of quinapril--a car accident, say--the plaintiff's attorney could argue that the deviation from community standard caused the seemingly unrelated event. There is too little experience with high-dose quinapril to refute the claim that, somehow, it caused the car accident.

Thus, an innovator is in the ridiculous position of not being able to use a new treatment for his/her own patients, that s/he knows to be safe and efficacious, until all other physicians adopt it, too. I reversed kidney failure in my first patient in February, 1994. High-dose quinapril has worked well for

the past 21 years. But nobody else is using the treatment yet, an interesting story in its own right (10). And I'm not allowed to practice my new treatment, even in solo practice. Insurance companies refuse to pay for the medication. Ref. 8 doesn't change their mind. They adhere to the community standard. It doesn't matter to them that the patient will go on dialysis and die prematurely after great expense.

Innovations must be given the benefit of the doubt, not suppressed. We cannot give in to fear, or else we will never improve medicine. Only a practitioner, or a patient or family member, can truly appreciate medicine's current inadequacy. Managed care executives, government and insurance bureaucrats, and non-practicing biomedical scientists have no concept of how urgent the suffering is out there. They don't have waiting rooms.

If an innovation prevents a horrible outcome, then experience must continue to be gathered with the innovation, until it is known definitively whether a seemingly unrelated event,

like a car accident, does occur more frequently with the new treatment. If so, we'll need to find another new treatment. If not, we've kept a lot of people off kidney dialysis.

Fortunately, people don't sue for improved clinical outcomes. There's no need for tort reform as long as there's sufficient evidence that an innovation works, that it's safe, and that it's superior to any alternative.

The best approach for Precision Medicine would be to target currently untreatable diseases with drugs known to be safe. New drugs should only be developed as a last resort, since they take so much time (10 years) and money (\$1B) to produce. Drug discovery currently starts in model systems, and concentrates on proving efficacy, largely to show that the model system is relevant to human disease. Drug toxicity is left to Phase III trials, which wastes time and money. Precision Medicine can invert drug discovery, since genomic epidemiology yields hundreds of drug targets, all derived from patients. Efficacy is assured. The important step now becomes sorting among these riches for the least toxic compound. This approach will certainly please the FDA.

Using old drugs requires a novel business model, that of Disease Management. Disease management companies make money by taking better care of sick patients than anybody else. They use nothing proprietary. Their time has finally come, since public and private insurance has to take care of many more people than before, and the cost is already too high.

Pharmacogenomics, the current form of Precision Medicine, is a waste of time and money. Thirty years ago, clinicians were perfectly comfortable dosing Coumadin without having to know a patient's CYP450 alleles. The DNA test is expensive (\$1,000), and the pre-test probability quite low. Very few patients bleed out during the first few loading doses of Coumadin. Any poor metabolizer can just be picked up with an early protime. So instead of waiting a week for a protime test, which costs \$5, get one on day 3 or 4 if you're worried. You have to follow protimes anyway.

NOS3 Promoter SNPs

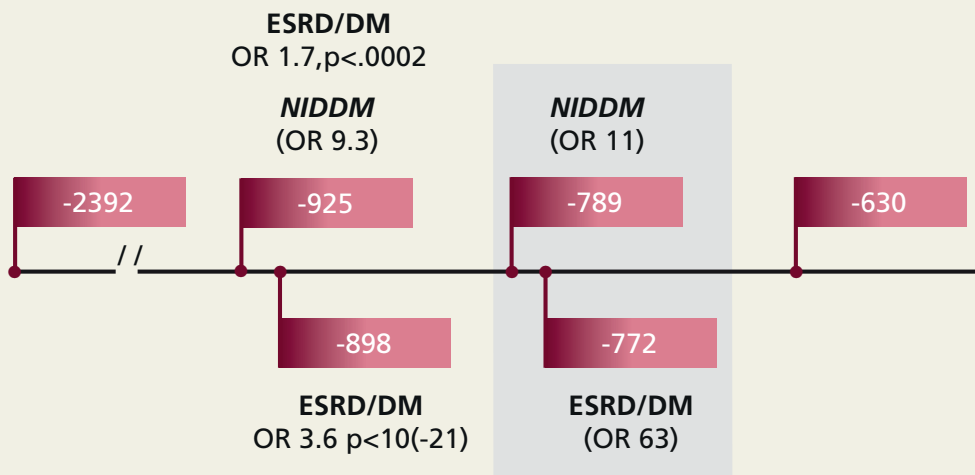


FIGURE 1: Evidence against linkage in polygenic disease. Numbering is according to GenBank Locus AX201792. The positions of SNPs upstream of the transcription start site in the NOS3 gene (on chromosome 7) are as follows: -2392 (150,988,664); -925 (150,990,131); -898 (150,990,158); -789 (150,990,267); -772 (150,990,284); and -630 (150,990,426). Odds ratios without p values are preliminary. Odds ratios with p values were

confirmed by genotyping 706 white male controls, 236 white men with type 2 diabetes (NIDDM), and 213 white men with diabetic renal failure ("ESRD/DM"; data from US Patent WO0153537). None of these SNPs are contained in dbSNP. Of special note are the SNPs at -789 and -772. Although only 17 bp apart, they have entirely different disease associations. They are unlinked.

For statins, just get liver-function tests (SGOT, SGPT, alkaline phosphatase; part of a standard “metabolic panel” costing \$50) after one month on the statin. You have to check LFTs every month or two anyway. A DNA test to see how the patient metabolizes statins is expensive and unnecessary, and should not be reimbursed.

How to fix the system

The missteps of Precision Medicine to date illustrate how concentrating power in the hands of the wrong people can waste everybody’s time and money. NIH has made a number of costly mistakes over the past 20 yrs. Discarded samples which are anonymized should not require informed consent. DNA is not sacred, certainly no more sacred than the patient. The NIH needs to make research in the US easier, not harder. Informed consent adds enormously to the cost of a project, allowing only the richest labs to perform research. Research needs to be more democratic, not less so.

If discarded, anonymized DNA could be studied without having to get informed consent, as was the case 20 years ago, there would be no need for \$215M just to bring existing biobanks at the Framingham study and NHANES into compliance. That money could be used for genotyping, which is job #1.

Medicare and Medicaid already have the data to link individual patient outcomes to the physicians who cared for the patient. CMS should aggregate and report this data for each physician (e.g. how many diabetic patients did physician A see last year? How many went on dialysis last year?) Patients would of course be anonymous, but not physicians.

This will do a number of good things that Obamacare tries to do but can’t. It will emphasize the importance of outcomes, which aren’t reported at all yet. It will engage all 700,000 practicing physicians, rather than wasting money on the same agencies that failed to prevent dialysis for the past 20 years, e.g. AHRQ, NIH, and the Secretary of HHS (8,10). The Patient Centered Outcomes Research Institute, established by Obamacare, has a great name, but spent the past two years, in typical bureaucratic style, just deciding how it is going to pursue research.

The usual insiders were asked for their input, and now, *mirabile dictu*, only they will be in a position to get grants.

CMS should compare the best clinical outcomes with the worst, and invite the best physicians to explain how they got their results. There is no evolution without underlying variability. Rather than enforcing homogeneity, as managed care does, we need to exploit the treatment variability in the country, as nature does. Some physicians have solved diseases already! I remember being invited to give a talk in Lubbock, TX on preventing diabetic nephropathy. A physician gently asked me what I did to prevent diabetes. I said “high-dose quinapril,” my answer for everything. It gradually dawned on me that he knew more about diabetes than I did. He’d worked out a beautiful plan for delaying diabetes that involved acarbose and then nystatin to prevent the diarrhea associated with bacterial overgrowth due to excess glucose delivered downstream. This is how we need to learn from one another.

Patients will vote with their feet. Reporting patient outcomes for each physician will help patients choose good doctors, just as CMS’s rating scheme is helping to improve dialysis care. To avoid losing patients (“marketshare”), physicians will finally be motivated to improve outcomes, something they’re terrified of even attempting right now. The rigid community standard will be a thing of the past, no legislation needed. No tort reform will be required. Physicians will have to produce better outcomes or perish. Lying about outcomes will be impossible, since other physicians will be claiming CMS payment also for the diabetic patient who winds up on dialysis or gets a foot amputated. The system will finally be patient-oriented.

FZD2 (Frizzled 2 is an oncogene in the Wnt pathway)

SNP	Chr.17 location	SNP type
rs7216125	44,556,909	promoter (535 bp 5’ to transcription start site)

Minor allele frequency: A=0.1318. The cancer-associated allele is the minor allele.

SNP	Breast	Colon	Lung	Ovarian	Pancreatic	Prostate
rs7216125	A,15	A,5.2	A,6.2	A,5.7	A,6.2	A,5.2

This SNP occurs at the 5’ end of a Pit-1a transcription factor binding site, ATGAAAA. Replacement of the A by a T destroys the Pit-1a binding site. The A allele should allow Pit-1a transactivation of the FZD2 gene, a known oncogene.

In this atmosphere, which could begin tomorrow, Precision Medicine could finally flourish. It must help patient care. Physicians will have an incentive to see if it could, rather than the current incentive to pad their wallets. True, we still don’t know who will pay for it. But at least it will be valued for the right reason. Instead of racking up charges for clinically irrelevant but reimbursed tests like cytochrome P450 SNPs, physicians will hopefully deploy only DNA tests that help the patient.

If NIH wanted to know what to do with its money, it could pay for DNA testing for the next 5-10 years, so Medicare could find out which DNA tests actually improved patient outcomes. If Congress can’t find any extra money, perhaps the NIH could shut down its intramural program, which has been an obsolete sinecure since at least the 1970s, when new medical schools were built with their own research facilities. Medicare could try to make the country dialysis-free, which has been possible since 1994, and which would save \$35 billion a year, not to mention keeping an extra 90,000 Americans alive each year, most of them people of color. To this end, the NIH’s NKDEP (National Kidney Disease Education Program), inside the NIDDK, should just do its job.

Imagine the places we’d go if the bureaucracy finally worked for the people it was meant to serve, instead of the bureaucrats themselves. Imagine making the Secretary of HHS’s job depend on whether patient outcomes improved during his/her tenure. That would empower the Secretary to stand up to prima donnas and harness the considerable power of the Department, including the CDC, NIH, CMS, AHRQ, PHS, etc., to improve the public’s health. No more science for science’s sake. If it didn’t help patients, out with it! Let the NSF fund it. What a happy day indeed for taxpayers and patients.