



To: The FDA

From: Population Diagnostics, Inc.

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**Subject: Oversight of Laboratory-Developed Tests (LDTs)
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In response to the U.S. Food and Drug Administration's July 19-20, 2010 meeting for public input on its oversight of LDTs, Population Diagnostics respectfully responds with the comments below. We hope the FDA proceeds thoughtfully and carefully as it aims for "reasonable and effective regulation to protect public health." Importantly, we request that the FDA, being an agency of the Department of Health & Human Services, not only consider its duty to protect but also to serve public health. We document below, with intentional redundancy for emphasis, details and context of new information fully understood by only a handful of disease researchers. This new knowledge is critical to understanding the key role that LDTs will play in the translation of new genetic discoveries into personalized medicine.

Background

Having reviewed the majority of transcripts, webcasts, and other documents relating to the FDA's heightened concern about genetic tests, which provide a background and set of opinions that may influence future LDT policy, we believe the FDA has not yet given consideration to a pivotal body of scientific evidence shaping the future of genetic medicine. We implore that you prioritize your attention to the information herein as it sets forth the dramatic shift away from long-held hypotheses on human biology and the genetic causes of disease. This newly emerging knowledge has immediate and broad implications for how LDTs are regulated. In fact, the FDA must pay attention to this recent and rapidly accumulating evidence as it directly impacts how diseases will be diagnosed and treated if we are to achieve the HHS goal for higher quality, lower cost health care. Further, we believe a comprehensive understanding of these scientific concepts may also shed light on the root of the controversy that has precipitated not only the FDA's concerns, but also those of health care providers and the general public about how genetic discoveries in the last decade are being presented.

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We assert that if the FDA were to fully understand the scientific evidence in the context of new genetic principles, it would recognize that changes to LDT policy are not only premature, but also would be an abandonment of core values on which LDT policy was established, which has successfully tackled unmet medical needs for many years. Additionally, we intend to point out that a misrepresentation of genetic discoveries has enabled commercial exploitation of the general public. Based on the information we present herein, we respectfully urge the FDA and other governing agencies to take decisive legal action to protect the public against those inappropriately exploiting genetic information, but without compromising an infrastructure that was established and implemented by a majority of genetic test providers to legitimately advance medicine. The FDA, CLIA, and the public are essentially unintended *and* intended victims of a decade-long scientific hypothesis that is now invalidated, and the lack of appreciation for the current findings on what causes common, complex diseases may unintentionally cause you to make stifling changes to the next decade.

What's New in Genetics – Common is Out and Rare is In

Genetic research and the methodologies employed for discovery have hinged for over a decade on the “Common Disease – Common Variant” (CD-CV) hypothesis. This theory was contested by a minority of scientists at the outset but as with any challenge of a broadly adopted scientific principle, it takes not only time for supporting evidence to mount for a new hypothesis, but also time for the prevailing hypothesis to play out. The inflection point between the prevailing CD-CV hypothesis and its opposing “Common Disease – Rare Variant” (CD-RV) hypothesis is upon us and is rapidly transforming the field of genetics. That is precisely why we emphasize the need to retain a primary purpose and spirit of CLIA LDT policy, which was, in large part, established to address rare diseases with unmet medical needs. Without continued government support and strengthening of the current LDT policy for genetic tests, Americans will have to continue to settle for substandard, high-cost, one-size-fits-all health care rather than benefit from truly individualized, low-cost health care that our world-class universities and biotech industry can deliver.

The main characteristics of the competing common disease hypotheses are as follows (for further details, see Bodmer W & Bonilla C, *Nat. Genet.* 2008 Jun;40:695-701):

CD-CV

- Common variants with population frequency typically >5%
- Low penetrance
- Odds ratios mostly <1.5

CD-RV

- Rare variants with population frequency typically 0.1-3%
- High penetrance
- Odds ratios mostly >5

In hindsight, it is regretful that a common disease was ever described using the word “common.” Historically, physicians have not had sufficient tools to differentiate subtypes of a common disease and thus they relied primarily on phenotypic characterization and classifications. Therefore, those with a common disease have been lumped together by phenotype without consideration of genotype. While most of us understand the concept of disease heterogeneity with regard to symptoms and progression, we may not fully appreciate what this actually means in terms of genetics. The reality is that a common disease is actually a collection of genetically distinct rare diseases manifesting as a similar phenotype. Some of these rare genetic causes have already been

identified within specific genes, including: BRCA1 and BRCA2 in breast cancer; APP, PSEN1, and PSEN2 in Alzheimer's; SNCA and LRRK2 in Parkinson's; and MECP2 and FMR1 in Autism. Yet these examples represent only a small fraction of the multiple genetic subtypes researchers expect to find.

It is critical to underscore at this time that the CD-CV theory, which was championed by many and served as the basis for the HapMap projects, has been laid to rest. The principal discovery method – genome-wide association studies (GWAS) using SNP microarrays containing a half million or more SNPs – failed to delineate the genetic causes of virtually all common diseases despite >600 published studies. Therefore, the vast majority of rare variants comprising the missing heritability of any common disease is today an unsolved problem but is on the verge of being solved. Further, we note that a common extension of the CD-CV hypothesis incorporates the polygenic theory, which posits that multiple genes, each of weak effect, are considered to be additive (positively or negatively). In contrast, in the CD-RV model, multiple genes can cause a phenotypically defined common disease but the genes (and the rare variants within them) will *individually* suffice, in most cases, to explain the disease in a given individual. That is, the “same” disease in different individuals can be caused by different, independently acting rare variants, which will often be in different genes and thus potentially involve unique biological pathways.

To summarize the genome biology we face in solving diseases and developing genetics tests and targeted therapies, existing or accumulating scientific evidence supports the following possibilities for disease phenotypes:

- Mendelian, caused by *one* gene with *many* rare allelic variants but with high penetrance
- Complex monogenic, caused by *one* gene with *many* rare allelic variants but with medium penetrance
- Complex multigenic, caused by *many* genes with each containing *many* rare allelic variants and with medium to high penetrance depending on the genetic subtypes found.

We suggest the adoption of new nomenclature as an attempt to redefine “common disease” as “complex multigenic” disease and to distinguish it from the often used term polygenic disease, which presumes accumulating burden of disease from gene-gene interactions. Such nomenclature does not imply that environment and epigenetics do not contribute to the manifestation of complex disease phenotypes, but the emphasis is on the notion that “common” disorders are actually an amalgam of rare diseases characterized by medium to high penetrance alleles. Further, we cannot forget that disease severity and progression are impacted by allelic heterogeneity within any given gene as some mutations are more deleterious than others (consider the hundreds of variants causing cystic fibrosis or muscular dystrophy vs. the hundreds of variants within those same genes that do not cause the disease!).

Human Diversity – Then and Now

When one considers the prospect that a common disease is in reality a collection of genetically distinct rare diseases, an entirely new perspective must be adopted on how to diagnose and treat disease. The following list, which summarizes new knowledge or key points to consider with regard to oversight of LDTs, is presented to the FDA in a general context as we know that exceptions exist or are possible:

1. The role of common variants in common diseases has been found to be minor, with only a handful of exceptions (e.g., the role of CFH in age-related macular degeneration, which incidentally was the first published genome-wide association study, appearing back in 2005)
2. A retrospective view of the adoption of gene discovery methods and research tools over the last decade reveals that the common variant exceptions promoted the use of these tools, as did the speculative opinions of highly respected researchers involved in the Human Genome Project.
3. The disease discovery tools and methods that have been used over the last decade were specifically designed to find common variants causative of disease, but these have not been found after having spent billions of dollars since the year 2000.
4. Genome-Wide Association Studies (GWAS) have yielded lackluster results despite over 600 studies for over 40 common diseases and traits. GWAS were designed to find markers (tag SNPs) linked to common variants causative of common diseases (CD-CV hypothesis). Instead, they have revealed markers linked to likely genetic modifiers that have been demonstrated to be statistically significant only on a population level (analogous to the way epidemiological studies have been designed). However, such markers are not the genetic cause of disease, nor can they be predicted to reside in the vicinity of the genetic cause within the genome (rather, they are in linkage disequilibrium with the “weak effect” genetic modifiers). In fact, fine-mapping of the SNP-associated regions, whether by higher density SNP scans or sequencing is unlikely to yield an appreciable number of causative variants.
5. The polygenic theory has been inappropriately and universally invoked over the last decade. It presumes that multiple variants act in concert (in a single individual) to explain disease differences such as age of onset, severity, risk, etc. GWAS have not yielded compelling evidence to support this theory and the general public has been misled on the ability of collections of common variants to predict existing or future occurrence of common diseases. Sadly, the failure of GWAS to uncover true causal explanations for common diseases has given genomics/genetics a tarnished reputation, with some incorrectly asserting that the disorders being studied have little genetic basis and genetic studies should be abandoned altogether!
6. There is now ample scientific evidence that rare genetic variants (often in the form of copy number variants) in different genes are capable of independently generating a common phenotype. Such recent scientific findings exist for a broad range of “common” diseases (e.g., Autism, Schizophrenia, Alzheimer’s, Parkinson’s, and Epilepsy).
7. When considering that a given disease can result from multiple, independently causal rare genetic variants (such that these variants may reside in different genes and each patient likely has only one mutation that is largely responsible for a particular disease phenotype), it becomes obvious why drug discovery has been largely unsuccessful (e.g., no increased rate in FDA approvals and a pharmacopeia directed at <500 of 20,000 potential gene targets). As biological pathways rely on the normal functioning of multiple genes, deleterious mutations in any of the relevant genes for a particular pathway may result in a similar disease phenotype. Thus, it should be no mystery why a good drug candidate is often only efficacious in a limited group of individuals imprecisely classified within a larger group based on phenotype alone. A drug designed to intervene in two or more unrelated pathways is a major, if not impossible, endeavor.

8. The failed common variant hypothesis is interwoven with several other misconceptions held for over a decade that profoundly impact our understanding of human genetic variation and thus our ability to develop sensitive, specific Dx tests and safe, effective drugs. These include:

(a) Individuals are not 99.9% genetically identical as originally estimated but this is still perceived to be true by many (including physicians and other clinicians) outside the field of genetics/genomics because it is widely cited in textbooks and on countless websites (including NHGRI webpages). In fact, the latest best estimate is that any two individuals are ~98.5% similar, which translates into a 15-fold increase over the long-held perception of human diversity.

(b) Human genetic variation is not only greater, but also more complex. It encompasses a much larger spectrum beyond just SNPs (1 nucleotide differences) and extends into several types and sizes (some as large as a few million nucleotides) of structural variants. One main class of structural variants are copy number variants (CNVs), which are frequently large enough to impact the gain or loss of whole genes (i.e., result in gene dosage effects). Importantly, structural variants such as CNVs often occur as *de novo* events in an individual's genome (i.e., are not inherited from either parent). Such *de novo* variants alone can account for appreciable non-Mendelian inheritance that is characteristic of common diseases (i.e., the “now you see it, now you don't” nature of “sporadic” forms of a common disease). Finally, in addition to the environmental impact on genes/genomes, we cannot forget the global architectural differences (genetic background) between genomes (e.g., subtle modifying effects on disease phenotypes from common and/or rare variants, incomplete penetrance, variable expressivity, and epigenetics) and differential biology at the RNA (e.g., alternative splicing and microRNA regulation) and protein (post-translational modifications, differential targeting within the cell) levels when accounting for the complexity of both rare and common diseases.

(c) Studying disease in homogeneous populations has also largely failed. Whether on a regional/national basis (e.g., Quebec founders in Canada, Icelandics, Estonians, and Finns) or religious/cultural basis (e.g., Utah Mormons, Amish, and Ashkenazi Jews), extensive studies over the last decade have yielded little insight into the causes of common diseases. With most of the companies using these populations now out of business, it is clear that their findings, had limited, if any, clinical value in broader, more diverse populations (or even in their narrow populations). Instead, it is now widely understood that a medically relevant genetic finding must be demonstrated in the population at large, which in most countries is already ethnically diverse or undergoing a rapid increase in ethnic heterogeneity.

The bottom line that the FDA must take into consideration as it contemplates changes to LDT policy for genetic tests is that interindividual variation is not 0.1% (3 million nucleotides), but 1.5% (nearly 50 million nucleotides). What this means from a retrospective viewpoint of disease research is that the discovery tools that relied on one reference genome (Human Genome Project) and a limited sampling of a handful of additional genomes (HapMap Project) do not take into consideration the vast majority of human variation. SNP microarray design, gene expression microarrays, GWAS algorithms, etc., are all flawed and therefore most genetic information produced over the last decade has not revealed the root causes of disease. We feel safe to say in hindsight, that such studies lack clinical value as they were based on a severely limited understanding of human variation and disease biology.

Two critical points that must be emphasized as a result of the new knowledge summarized above when developing new genetic tests (or new drugs) with sufficient clinical validity and utility in health care are:

1. The greater spectrum (extent and complexity) of genetic variation dramatically changes our views and assumptions not only in disease biology but also normal biology. In other words, when establishing the causality and functional significance of any single genetic variant, it must be done with a thorough understanding of what is normal.
2. The reality of a common disease being genetically dissected into multiple rare subtypes, particularly if the causative variants/genes are impacting independent biological pathways, will dramatically alter currently envisioned formats and content of LDTs developed for genetic testing (both for disease prediction/progression tests and companion tests). That is, with regard to clinical validation and/or clinical trial design, in many cases there will simply not be enough cases to test using existing or planned FDA guidelines.

Personalized Medicine – It’s the Causality...

In the interest of connecting the dots, we reiterate our message to the FDA and simplify it for those that are not genetic researchers or clinicians: diseases such as Autism, Parkinson’s, Alzheimer’s, Schizophrenia, Bipolar Disorder, Diabetes, etc., *are not common diseases but rather are an amalgum of rare diseases that have not yet been genetically resolved*. For example, Parkinson’s may eventually be genetically subtyped to Park1, Park2, Park3, etc., because these forms of the disease correspond to Gene1, Gene2, Gene 3, etc. Similarly, Park1 may be further dissected into Park1A, Park1B, Park 1C, etc., because these subtypes correspond to different rare variants within or impacting the expression of Gene1.

Classification of rare subtypes is a prerequisite for accurate diagnosis and new therapies to be rationally developed. This should not be a novel concept to those educated in medicine where a classic example can be cited in the field of cancer. In 1950, one may have been diagnosed with a “blood disorder” because clinical phenotypes could not be differentiated. In 1960, that same diagnosis was differentiated as either Leukemia or Lymphoma. Today, in 2010, Leukemia comprises >40 different rare subtypes and Lymphoma comprises >50 different rare subtypes. We hope that the FDA agrees that this field of medicine is considered today one of the most successful diagnostic and treatment arenas because of successful subtyping of blood disorders. Interestingly, cancer is still referred to as a “common” disease and regrettably we consider this terminology as having an adverse effect on widening the perceptual lens for other complex diseases that are presumed to be common. This highly successful and still evolving disease model is put forth to make the point that it is still “1950” for most other common diseases as they have not yet been resolved into their rare subtypes. Only when each rare subtype is known and each can be diagnostically tested for, will there be a way to rationally develop drugs and systematically select the right patient for the right drug.

When LDT policy was established in 1988 under the CLIA statute, in large part, it was designed with rare diseases in mind so that these underserved patients would have an opportunity to receive personalized medicine. The words “personalized medicine” did not exist in those days, but in our review of references, including a presentation by an FDA official at the recent LDT public hearing, personalized medicine was indirectly described in the context of addressing unmet medical needs for rare diseases. It is on this point that we believe the original framers of LDT policy had it right from the start.

In the 1990s, leaders of the Human Genome Project justified the scale (concentration of effort in a few large academic labs) and financing of the project by explaining that the knowledge will deliver to medicine the “causes” of disease as well as explain the efficacy and safety of drug response (pharmacogenomics). We, like most of our colleagues, believe it was a good decision to sequence a human genome. However, there are an abundance of industry influences that have caused an entire decade of science to have gone off track. Consequently, the public has been disappointed and misguided. On the simplest level, the primary problem is that the “cause” of disease has not been found. The explanations for drug efficacy and safety have not been found. On an execution level, it can be stated that the vast majority of genetic findings for complex diseases originating from either SNP-based GWAS (again, there have been >600 published studies!) or via gene expression profiling lack medical relevance and therefore lack clinical utility. To reiterate, the goal of the Human Genome Project was to find causes of disease – regretfully, most causes have not been found.

In some industries, it might be acceptable to settle for less. For example, if high quality crude oil is expected to come out of a well, but in actuality the oil is lower quality than expected, the oil can be further refined or redirected to products with lower quality specifications. This is not the case with medicine. If information lacks a high degree of medical certainty, it will not be used by physicians to diagnose and treat patients because low quality genetic information will not be medically actionable, or worse, could be life-threatening.

Most of us understand what genetic causation means because there are an abundance of examples where diagnosis is primarily made via genetic testing at the single nucleotide on up through the whole chromosome level. We note here only a small subset of the thousands of diseases for which there are genetics tests available: Down syndrome, cystic fibrosis, muscular dystrophy, Ashkenazi Jewish disorders, hemophilia, etc. Yet, most genetic research of the last decade has delivered something that does not resemble what we have become accustomed to and as a result physicians are not adopting it. Simply, and restated here in the context of medical relevance, the problem is that the vast majority of GWAS-derived genetic information being offered in the marketplace (via health care providers or the direct-to-consumer route) cannot be considered causal of disease. These GWAS-derived genetic variants are not what was promised but instead yield genetic information characterized with words such as “risk factor,” “predisposition,” and “susceptibility.” We believe usage of such terms is an attempt to get physicians to settle for medically uninformative “markers” of disease, which at the same time leads to confusion and unnecessary alarm in patients.

Unfortunately, medicine does not yet have a formal resource for clinical validity and medical relevance of genetic tests. While the NIH is initiating establishment of such a resource (Genetic Testing Registry), there are several concerns among professional stakeholders (e.g., ACLA, ACMG, AMP, ASHG, and CAP). To date, the medical community (broadly including doctors, lab directors, genetic counselors, hospitals and clinics, diagnostic and pharmaceutical companies, biomedical research institutions, etc.) have generally recognized that biomarkers – defined herein to include genetic proxies or actual causative variants of disease or drug response – should yield measurements with certainty. Physicians should be applauded, and their sophistication should be appreciated, for not adopting genetic biomarkers that lack clinical utility; nor are they widely using genetic information that lacks medical actionability. To us, this is clear evidence that current LDT policy works. CLIA-certified laboratories customarily operating in the field of medicine are not among those precipitating a need for more LDT regulations/oversight. They are, in fact, particularly instrumental in serving the diagnostic needs of patients with rare diseases and in clarifying the requirements for medicine. Further, market forces alone, driven by current day standards, decide whether an LDT is developed and adopted.

The FDA's concerns about existing LDT policy as it pertains to genetic tests are valid, but we draw attention to the fact that most CLIA labs and the genetic tests they offer serve doctors and their patients very well. It is only a very small number of labs offering and promoting tests of little to no medical value that are jeopardizing the LDT system. As summarized and discussed herein, most genetic findings from the last decade – namely, common variants from GWAS – are not causative of disease. However, direct-to-consumer (DTC) companies have emerged as a user of this information because they genuinely believed the genomic research community (i.e., those who revealed and presented the information in peer-reviewed journals) that these genetic markers had value. Further, the rush to market was exacerbated by hype from the Human Genome and HapMap projects and because this genetic information was freely available (i.e., unhindered by licenses), as it was federally supported research mandating deposit in the public domain and timely publication. In some cases, medical value had been ascribed to the genomic discoveries and academic institutions created an even higher value for them through a licensing program.

Regardless, what we are experiencing today via the DTC industry is the result of flawed science that was promised to be translational. We reserve judgment of the DTC industry and believe it does empower individuals to learn about themselves and family (e.g., ancestry testing). Despite the irresponsible use by some labs of clinically useless genetic markers, we do not support further regulatory guidance or action from the FDA on LDT policy. We expect that testing for most of these common variants will fade into obscurity when truly causal rare variants (i.e., those properly vetted by a range of criteria well-established in the research and medical communities) emerge from the next phase of genome research.

Concluding Remarks

Do causative rare genetic variants for common, complex diseases exist? [In other words, do we need LDTs to diagnose common diseases?] Yes, as noted above, causative genes have been identified for the so-called rare forms (i.e., affecting only a few percent of patients) of several common diseases. More recently, rare CNVs with odds ratios ranging from 5-70 have been identified for common diseases (e.g., Autism, Epilepsy, and Schizophrenia). However, the majority of rare variants are yet to be found but it is anticipated that they will comprise much of the “missing heritability” (*Nature*. 2008 Nov 6;456:18-21). Our company is just one of a handful of R&D groups with a strategy and methods to systematically reveal comprehensive collections of genetic rare variants for disease. But with the growing number of disease researchers shifting focus from common to rare variants and the rapid advance of DNA sequencing technologies, a deluge of disease-causing genes and the many variants within them will soon be upon us. Thus, the need for LDTs has never been greater!

Can every person's complex disease be characterized by a rare genetic variant? No, but for those who can, their genetic subtype can be diagnosed with high certainty when appropriate metrics of causality are established (e.g., high odds ratios, replication in additional disease cohorts, functional studies supporting pathogenicity of the causative mutation, etc.). For those that cannot be genetically subtyped, their disease should be considered an unsolved problem, which may eventually be resolved with other types of information (e.g., environmental and epigenetic factors) or non-genetic diagnostic criteria.

In light of a complex disease being considered a collection of rare genetic diseases masquerading as a common phenotype, bringing each diagnostic test to the market can mirror current and effective strategies already in place for rare diseases. If the FDA, without comprehensive education on the new genetic principles described herein, were to make any changes to LDT policy – attempt to

define validation standards, apply risk scores or control population statistics, require costly (time and money) design control methods, etc. – because you are compelled to do so by a failed decade of genomics, we maintain that you will inadvertently stifle the next generation of diagnostics and therapeutics for complex genetic diseases.

Population Diagnostics is a commercial leader in deploying the rare variant hypothesis to solve common diseases. We believe we know every thought leader and expert in the field who understands the promise of rare variants and thus know with great certainty that the FDA does not comprehend the full extent and import of this new knowledge. Neither does the pharmaceutical industry. We caution consulting with the numerous stakeholders in the common variant hypothesis who may not be up-to-date on the compelling evidence for rare variants, are unwilling to acknowledge their failed assumptions on disease causality, or are irresponsibly pushing DTC genomics. We urge you not to amend LDT policy before becoming educated by: 1) those with expertise in rare variant research and state-of-the-art genome discovery methodologies, and 2) those operating CLIA laboratories with extensive experience developing LDTs for genetic testing of rare diseases or rare mutations of “common” diseases. Not hindering the translation of thousands of disease-causing rare variants that are on the horizon into diagnostic tests (and drug discovery pipelines) is the only way the USA can be a leader in personalized medicine, which is the future of safe, effective, and affordable health care.

Thank you for providing a forum for public input and feedback and your attention to our comments.