



Commentary

Precision medicine is here, break out your wallet

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Every article I have read, and just about every conference I have attended, in the past couple of years has proclaimed the arrival of precision medicine. 'Precision medicine is finally here!' This is the message that pervades the media outlets – from online industry journals to the *NY Times* – each snapping up the sound bites from genomic pioneers bent on revolutionizing health care. This implied revolution is brought upon by the continued advancement of next generation sequencing technology and the associated rapid decline in the costs of sequencing sections of a person's genome.

There is only one problem with these assertions; they never seem to discuss the economic reality of our healthcare system. Who is going to ultimately pay for the precision diagnostics required to unlock precision medicine? Health insurance companies or Medicare? Both? Unless the clinical utility of the test has been well established, I would not count on it. Because of this hurdle, when it comes to new test adoption, commercial payers are usually the last ones to board the bus. Pharma companies? Maybe. They might pay for a companion diagnostic if the cost of treatment is in the many thousands of dollars. But then who pays for the drug? And if a drug won't be paid for, what good is having the test? So who does that leave? Well, you and I, the patient. And just to be clear, when was the last time you rushed out to insist your doctor order an informative, yet perhaps not absolutely medically necessary test that you knew would cost you thousands of dollars?

2013 was a particularly poor year for the future of precision medicine. While technology announcements that the '\$1000 genome has arrived' dominated the major genomic news stories, you will have to turn your attention to Wall Street to get the real scoop. Flip through the earnings reports of some of the publically traded companies that offer genetic testing and a pattern will start to emerge – significant financial losses and statements about 'reduced Medicare reimbursement, Medicare non-payment, and CPT 2013'. Many genetic testing companies derive a significant amount of their revenue from Medicare and commercial insurance testing. Away from the headlines, the lesser-known fact is, with the exception of certain well characterized testing with specific Current Procedural Terminology (CPT) Molecular Pathology (MOPATH) codes assigned – e.g. cystic fibrosis and BRCA, Medicare significantly reduced payment for genetic testing in 2013.

So, what is CPT 2013? Medicare issues its coverage decisions annually based on the CPT guidelines developed by the American Medical Association (AMA), and Medicare contractors such as Palmetto who price these tests. In 2013, there was a restructuring of how genetic testing is reimbursed. Prior to 2013, most laboratory developed test (LDT)

genetics labs were utilizing CPT codes for billing that did not implicitly specify which test was being run on a sample for a specific disease, rather it was based on the methodology of a particular assay. For example, the following would be one way to bill for a test that screened for 23 mutations in the cystic fibrosis gene in 2012.

CPT 83891 – Molecular diagnostics; Isolation or extraction of highly purified nucleic acid

CPT 83892 – Molecular diagnostics; enzymatic digestion

CPT 83900 – Molecular diagnostics; amplification of patient nucleic acid, multiplex, first two nucleic acid sequences

CPT 83901 ($\times 21$) – Molecular diagnostics; Isolation or extraction of highly purified nucleic acid (21 times)

CPT 83909 – Molecular diagnostics; Separation and identification by high resolution technique (e.g., capillary electrophoresis)

CPT 83912 – Molecular diagnostics; Interpretation and report

CPT 83914 ($\times 23$) – Mutation identification by enzymatic ligation or primer extension, single segment (23 times for each mutation)

[2009 CPT code definitions: <https://www.businessgrouphealth.org/pub/f2f5b070-2354-d714-5166-07929500fea8>.]

This process of 'stacking' codes was the only method labs had for billing genetic testing. In the above test, the charges were for extracting and digesting the DNA, amplifying it, sequencing, identifying the mutations, interpreting, and reporting. You'll notice that nowhere in those codes does it identify the genes that are being isolated and sequenced or for which condition.

Payers have historically had limited transparency beyond the description that some test was performed involving some molecular diagnostic techniques on a patient sample and 23 mutations were reported on. Whether this gene, mutations, or even the test itself was relevant for the disease condition was anybody's guess. Determining if the test that was run on a patient had clinical utility from this obfuscated coding mechanism was a dead end. Payers would often reimburse for these tests without knowing what exactly they had paid for.

Enter CPT 2013 – gone was CPT code stacking, replaced by coding based on the number of exons sequenced or a specific CPT code for a specific genetic disorder. CPT 2013 created a precise code for cystic fibrosis gene analysis, so the previous example of stacked codes was simplified to this:

CPT 81220 – CFTR (cystic fibrosis transmembrane conductance regulator) (e.g.,cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)

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Commercial payers and Medicare now know which condition is being tested for and can now easily and quickly determine if the test or methodology for a specific condition falls under their coverage policies.

The issue for clinical labs is that very few genetic conditions have CPT 2013 codes specifically assigned to them and new disease causing variants for heritable conditions are discovered daily. While advances in our knowledge of diseases and their genetic underpinnings accelerates at break neck speed as sequencing costs drop, new CPT codes based on these findings often take significantly more time.

Most labs' test menu far exceeds the limited scope of a handful of conditions that have assigned CPT codes — especially for labs that test for rarer genetic disorders. Diagnostic labs have no choice except to bill these tests for CPT 81479 — Miscellaneous molecular pathology procedure. Now that payers have some insight into genetic tests with defined CPT codes, the chances that they would go back to paying for miscellaneous genetic testing was close to 0%. Indeed, Medicare payment for 81479 in 2013 was 0%. For the codes that are being reimbursed, in many cases, the new reimbursement rate associated with CPT 2013 is insufficient to even cover the cost of testing. This is creating financial pressure on many diagnostic laboratories and a number are at high risk for bankruptcy (<http://www.darkreport.com/PDF/Low-2013-Molecular-Test-Rates-May-Bankrupt-Some-Pathology-Labs.pdf>).

If you'd like to make a more informed assessment on whether 'personalized medicine is here', visit the website of just about any health insurance carrier and read through the coverage policies on genetic testing. You will quickly acquaint yourself with the phrase "Experimental or Investigational" that pervades this section for just about every conceivable genetic test that exists. All these tests suffer from what the payers cite is "a lack of clinical data to permit conclusions on clinical utility and net health outcomes".

Payer adoption of genetic testing and the reimbursement environment is lagging far behind the technology. Payers often require numerous studies citing the clinical evidence of a particular diagnostic test to appropriately assess its clinical utility before they decide to cover it for a given condition. Take for example chromosomal microarray testing for patients with developmental delays or autism spectrum disorders — payers are only now starting to issue coverage for this test, a full four years after American College of Medical Genetics (ACMG) issued a guideline recommending it as a first tier test for these patients (Miller et al., 2010).

Clinicians are not without blame, they oftentimes do not take the time to justify the medical necessity of a genetic test for a particular patient, document the clinical presentation and symptoms of the patient, or submit the proper ICD codes. The majority of denials from payers for even covered tests come from a lack of proper documentation by the ordering physician.

If payers are not blazing trails towards the future of precision medicine, then perhaps some combination of advocacy organizations, pharmaceutical companies, and associated companion diagnostics will get us closer. There are already a number of therapeutics that require a genetic companion diagnostic test assaying specific gene mutations before a doctor can prescribe the drug. Kalydeco™ is a drug developed by Vertex Pharmaceuticals for cystic fibrosis. It is only effective for the estimated 4% of cystic fibrosis patients who have a specific CF gene mutation called G551D (<http://www.cff.org/treatments/therapies/kalydeco/>). While Vertex does not provide the testing, they have collaborated with

the Cystic Fibrosis Foundation, which has a Mutational Analysis Program that provides free genotyping for people with cystic fibrosis.

In the near future, plummeting sequencing costs combined with increasingly genotypically focused drug targets may pave the way for a model where pharmaceutical companies pay for the gene or possibly full exome sequencing of patients before they are prescribed specific medications. This application will likely first appear in rare disorders and companies offering treatments for those conditions where therapeutics can cost hundreds of thousands of dollars annually. Paying \$1000 for a genetic test for patients en masse is not out of the question when the return on investment in collected pharmaceutical revenue can far exceed that initial cost. The prospect of giving pharmaceutical companies open access to your genetic information may not be palatable to many people, but for those with loved ones with a debilitating genetic disorder and mounting medical bills, this would likely not be distasteful in the slightest.

So what does this all mean for health care and precision medicine? There are many pretty charts that show the DNA sequencing cost curve compared to Moore's law. However, unless the healthcare industry is relying on patients ponying up thousands of dollars to have their genomes sequenced, I am afraid we are farther from when genetic testing will be a routine part of healthcare than most of us suspected, or would like. Right now, personalized medicine could be here for those willing to shell out for it. For the rest of us, the genetic revolution has been delayed while policy catches up with technology.

This gloomy outlook does not however mean that genetic testing has no future in medicine, quite the contrary. There are significant examples of how it can dramatically impact patient care. A child with a certain type of epilepsy exhibiting daily multiple seizures could be effectively diagnosed and treated. A genetic test could indicate that the child has a mutation in the SLC2A1 gene which codes a protein that moves glucose in and out of the brain. Treating the child with a high-fat ketogenic diet can almost immediately stop the seizures (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3152152/>). Thus, genetic testing can be a powerful tool in a clinician's arsenal when utilized appropriately. However there is much education and major policy work that needs to take place before it becomes widely accessible.

Disclaimer

The views expressed in this article are those of the author and do not necessarily represent the views of, and should not be attributed to, Quest Diagnostics.

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