COMMENTARY: Individualized medicine vs. precision medicine

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HERE ARE PEOPLE who will die of cancer this week even though there are drugs that could help them.

At the same time, hundreds of patients will undergo cancer chemotherapy that, while debilitating and expensive, will not cure them of their disease.

While cancer is a formidable foe, there is a way to improve patient care and prognosis immediately.

Researchers in Finland, Sweden and Spain have modified ex-vivo testing of cancer cells with significant results. Their approach is far more "personalized" than traditional precision medicine. Their results are striking. They provide a missing link between genomics-based mutation determination and clinical efficacy.

Precision medicine (also referred to as "personalized medicine" or PM) appears to many patients, doctors and researchers to be a golden highway from disease identification to cure. The idea of interrogating the genome of a particular cancer to determine its Achilles heel is intuitively satisfying and understandable. There are, however, significant problems. First, PM is neither personalized nor precise. PM strives to identify the appropriate biomarker (usually a DNA mutation but proteins, peptides and metabolites can stand as biomarkers as well) to categorize the patient as a member of a specific group of patients. The patient is treated with a drug that has shown positive results on previous members of the group. In other words, personalized medicine is actually population-based medicine.

In contrast, the method described by researchers at the Institute of Molecular Medicine, Finland, determines empirically the best treatment with what they call "individualized" medicine to differentiate it from PM. They follow the determination of the appropriate therapy with detailed genomics-based analyses of the patient and the cancer to develop an understanding of the mode of action of the therapy. By integrating the cure with an understanding of the genetic mutation, they have changed the existing paradigm and created "individualized system medicine." The power of the individualized system medicine approach includes the ability to more quickly look at mechanisms of action, assess drug combinations, understand drug resistance, position and de-risk drug candidates and provide more rapid drug repositioning in a way that has not been previously achievable.4

There are three critical problems with genomics-based PM. Two of these problems are intrinsic to the biology. Genomics-based science has identified exciting new methods of treatment and I do not call for its abandonment, but rather adding to the process the critical step of ex-vivo testing to mitigate some of the deficiencies inherent with genomics approach alone.

Problem 1—Mutations in DNA are not clear signs of the cause of the cancer (or disease)

Typically, genomic analysis is used to determine what mutation causes the cancer. Sometimes the therapy works and at other times, the patient goes through debilitating chemotherapy only to find that there was no impact on the cancer. In fact, the cancer may have grown and further mutated during the time of the treatment, gaining both mass and genetic changes so that it is even harder to treat with supplementary rounds of chemotherapy.

While it may seem obvious that if you sequence the tumor and find the genetic flaw that causes the cancer, addressing that flaw specifically should result in remission. In fact, this desired outcome is sometimes achieved. Yet despite the apparent causal relationship between mutation and cancer, clinicians often do not see a good correlation between the identification of the genomic mutation and successful treatment.

Researchers at the Wellcome Trust Sanger Institute and their colleagues have observed that healthy skin tissue—tissue that appeared normal by any measure—was full of somatic DNA mutations. DNA mutations in the apparently healthy skin were found at the same level as the mutations in tumor cells. Not only did a quarter of the healthy skin cells carry a cancer-causing mutation, but the researchers found that these mutations were under strong positive selection—that is, the number of cells carrying the mutations tended to increase even though there was no evidence of cancer. This means that when an oncologist finds a cancer-causing mutation, it may not be the cause of the cancer jeopardizing the health of the patient. It may just be along for the ride. But giving a drug targeted to the harmless mutation delays getting the drug that will actually stop the cancer. All the while, the initial cancer drug may cause damage to healthy cells.

Similarly, researchers at Johns Hopkins showed that DNA analysis of tumor cells tended to produce many false positives. They suggest that comparing the mutations in apparently healthy tissue with that of the tumor will determine the true, cancer-causing genes. Unfortunately, the data from the Wellcome Trust Sanger Institute mentioned above suggests that healthy tissue contains many different mutations, and it is unlikely that there is a single healthy genotype to use for comparison. Simply put, evidence of the existence of a mutation is not evidence of a cause for cancer. Treating a patient based on a latent mutation may harm the patient and delay helpful treatment.

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Problem 2—Inability to reconcile genomic data and phenotypic results

Two extremely good labs, the Cancer Genome Project and the Cancer Cell Line Encyclopedia, analyzed the DNA of hundreds of different cell-lines. They also tested the cell lines against many different drugs to see how they responded. The data from both labs was analyzed by Quackenbush and colleagues, who found that their genomic results were spot-on. Both labs obtained very similar results when they analyzed the DNA from the same cell lines. However, when these labs tested identical drugs against these cell lines, they obtained dramatically different results. If one lab found that a particular drug was effective against a target in a cell line, the same analysis in the other lab, more frequently than not, gave contradictory results.

This means that even if finding DNA mutations meant that you could choose a particular target or enzyme to block in the treatment of a cancer, you might not be able to choose the right drug. Each lab could end up choosing a different treatment due to the difficulty in determining the correlation between drug and response.

It is important that the two labs obtained almost identical results in their DNA analyses. This shows that they both use consistent scientific methods that others can replicate. One assumes that if they can match results analyzing DNA, they should also be able to get equivalent results in drug response experiments. The fact that they do not suggests that the problem is not something as simple as competence in scientific technique.

A recent publication in *Nature Biotechnology* highlighting that certain individuals are resilient to Mendelian childhood diseases despite clear genomic evidence of the presence of the specific mutation is just another example of DNA sequence alone not providing sufficient proof of disease. This paper amplifies the impact of problems 1 and 2.

By adding critical information, the ex-vivo individualized systems medicine approach eliminates this problem and reproducibly generates the best therapy for a patient’s particular cells.

Problem 3—Personalized medicine falls back to guessing if no drug has previously been found effective against a cancer associated with a new genomic mutation

Assuming that you correctly determine the mutation causing the cancer among all the other somatic mutations in the sample, you may find a mutation for which no chemotherapy has been determined. The pharmacogenomic process can point you only to treatments that have already been verified. That means that the drug of choice has been tested in double-blind experiments and has gone through the required government licensing procedures for that particular cancer. While the number of therapies continues to grow, the personalized medicine pathway would miss (and would never even look to try) that some cancers can be cured by drugs not associated with a particular cancer. In essence, you would need to test all drugs against all cancers, a herculean feat with most existing protocols. Personalized medicine would not have pointed a doctor to using thalidomide or methotrexate against particular cancers, but individualized systems medicine can help uncover new uses for existing drugs in an orderly way. For example, researchers at the Institute for Molecular Medicine, Finland (FIMM) have shown that the antiangiogenic renal cancer drug axitinib can be repurposed against T315I-mutant BCR-ABL1-driven leukemia.

*Guessing is still just guessing even if there is genomic data. Having phenotypic results that show which drug or drug combinations kill a patient’s particular cancer is a significant advance.*

A Reasonable, Cost-Effective Complement to Genomics-Driven Testing

Finding a mutation does not necessarily mean finding the cause of the cancer. And even if the cause of the cancer is identified correctly, it is not easy to determine which drug will be effective against that mutation. What is the alternative?

Researchers at FIMM and elsewhere have turned the question on its head. Instead of trying to identify a mutation in the DNA and then trying to find a drug that addresses that mutation, they isolate cancerous cells from the patient. They then test those cancerous cells against hundreds of possible drugs to see which drugs are effective against the cancer. In some cases, they use cocktails of
drugs to see if the combinations are more efficacious than single drugs. They frequently test the drugs at many different concentrations to better understand the potential dosing aspects.

Just because a drug works against isolated cancer cells ex vivo does not necessarily mean that it will work inside the body. However, the inverse of that statement, that it does not work on cells ex vivo it is unlikely to work in the patient, is most likely true. This is what the researchers found. By screening the drugs against the patient’s cancer cells, they found other cancer drugs that were able to drive the cancer to remission while saving patients from ineffective treatments. Most significantly, this was true even in patients who had already failed multiple rounds of chemotherapy.

Chemotherapy has both monetary and health costs whether or not it leads to a cure. First-line treatments can fail and force the patient to alternatives. Every new round of treatment eats away at the window of opportunity to cure the disease.

The researchers at FIMM have developed an empirical, individualized test that can screen hundreds to thousands of drugs against a patient’s particular cancer quickly and at low cost. The test can eliminate chemotherapy that is highly likely to fail and it informs the clinician of the best options. With DNA analyses, as they describe in their papers, individualized systems medicine can help expand the understanding of cancers and guide future drug discovery.

While labs in Finland, Sweden and Spain are already investigating the technique, more labs should be moving this forward. As a member of a family that has been struck multiple times by cancer, I hate to think that I would need to book a flight to Finland in order to get the best options for chemotherapy.

Testing drugs for efficacy before starting chemotherapy will reduce costly but futile rounds of therapy. It would also identify active drugs and let the patient and doctor make secondary decisions on price. This could increase competition and drive down prices, especially on those drugs that show little if any efficacy.

While PM may give lip service to non-genomic assays, by far the greatest effort and the largest number of dollars are being directed towards using genomic markers to determine healthcare. In part, this is because the success of the Human Genome Project. Excellent scientists from the NIH, NCI, academia and private industry combined to provide the first full human DNA sequence. The question then was, “What’s next?” With hundreds of sequencers purchased and thousands of molecular biologists now trained, how could all these resources be put to good (and desired by the public) use? Healthcare was the obvious choice. But to the hammer, everything is a nail.

I believe that there is a role for genomic analyses in healthcare, I just do not think that it will be the panacea that many suggest. I am especially concerned that excellent tools, like those developed by FIMM, are not being used by researchers locked into solely the genomic pathway.

I urge clinicians and researchers to explore the work begun in Finland. The procedures are straightforward and the results can be rapidly available. The technique offers the promise of increased remissions, reduced failure of chemotherapy and decreased healthcare expense. A multilevel winning strategy uniting ex-vivo testing with genomics-based analyses appears within our grasp, and we need to take hold.

**REFERENCES**