Clinical testing should be individualized, not based on populations

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Biomarker discovery is one of the fastest growing fields in clinical diagnostics. A biomarker is defined as “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease” (1). Oncology, neurodegenerative disease, cardiovascular disease, and infectious disease fields are all exploring biomarkers for early detection, recurrence, and therapeutic monitoring. For example, discovering biomarkers for cancer using circulating tumor DNA is one of the most active areas, because tiny amounts of tumor DNA can be detected in blood by deep sequencing (2). Normal values are based on population measurements. Traditional clinical laboratory tests have a normal range associated with each analyte measured. For example, nonfasting glucose should be in the range of 70–110 mg/dL, LDH in the range of 50–200 U/L, and cholesterol levels should be below 200 mg/dL. The ranges and recommended levels constituting “normal” have been determined by measuring thousands of subjects over time. Even so, we recognize that there is a problem with such absolutes. In response, we define borderline levels for which the values are near to the normal range but are not high or low enough to diagnose patients with disease. Prediabetes and borderline high cholesterol are good examples. In these cases, such borderline measurements may be useful in recommending […]

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Biomarker discovery is one of the fastest growing fields in clinical diagnostics. A biomarker is defined as “a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease” (1). Oncology, neurodegenerative disease, cardiovascular disease, and infectious disease fields are all exploring biomarkers for early detection, recurrence, and therapeutic monitoring. For example, discovering biomarkers for cancer using circulating tumor DNA is one of the most active areas, because tiny amounts of tumor DNA can be detected in blood by deep sequencing (2).

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Baseline measurements are essential with more sensitive measurement technologies

With the advent of newer technologies that can measure exceedingly low concentrations of nucleic acids (mRNAs, microRNAs) and proteins, we are discovering new biomarker candidates. In many cases, these molecules vary over a hundred-fold in concentration and, in some cases, over ten thousand–fold between ostensibly healthy individuals (5). How is this variation biologically possible? Biology is robust, and when one component in a system is perturbed, compensatory changes to maintain homeostasis occur in other pathways (6). For clinicians used to having normal ranges that vary by several-fold, it is exceedingly difficult to define “normal” when patient protein values can vary by over a thousand-fold. Additionally, it is possible that biomarker distribution in a population may be skewed rather than normally distributed. This variability means that sick individuals likely will have biomarker values that completely overlap with those of healthy controls. Disease will be noticeable only by observing changes in these values within individual patients.

Baseline measurements will become even more challenging as we begin to incorporate protein and nucleic acid panels into medical diagnosis. By measuring many different species simultaneously and coupling these panels with computational or machine learning algorithms (AI), it is possible to identify patterns of biomarkers where the absolute concentrations are unimportant but the relationships between biomarkers are diagnostic. Such panels, coupled with these algorithms, overturn conventional approaches, because, in most cases, the values of all the biomarkers constituting the panel fall within the range of healthy individuals. It is the pattern of biomarkers that distinguishes healthy from diseased individuals, not the particular values of a given marker.

Longitudinal sampling is required for precision diagnostics

We can no longer rely on normal ranges for many of these new biomarkers. Each person has a healthy baseline. Their present self should be compared to their previous healthy self rather than to a population average. Variations in baseline levels will need to be understood over time — what is the normal variability of a particular protein within an individual over the course of a day, week, year? How do baselines
Biomarkers should be measured that indicate that the patient is moving away from a healthy state and returning to a disease state. Again, these changes would be individualized — what constitutes a healthier state for one individual might overlap with an unhealthy state for another.

In addition to the benefits to diagnosis, the information obtained by measuring biomarker values over time will likely lead to better mechanistic understanding of the pathobiology and disease pathways. In turn, improved understanding will lead to rational therapeutic interventions. By looking at high-resolution changes within an individual as they progress from good health to illness and then ideally return to their healthy baseline over time, rather than looking at differences from a population average, the perturbations should be clear and informative biomarkers can be identified.

The ideas proposed here will not lead to discoveries overnight because the underlying research will require a commitment by clinicians, researchers, and a large number of patients to procure blood, urine, and other samples over a long time. This approach differs dramatically from studies in which patients with particular diseases consent to provide a single blood sample and comparisons are made between healthy and diseased patients to identify the biomarkers that correlate with disease — the population approach. We need to commit the time and resources necessary to identify the meaningful biomarkers that correlate with disease and health within individuals to truly realize the full potential of precision medicine.

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