ORIGINAL ARTICLE

Moreton Lecture: Imaging in the Age of Precision Medicine

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Abstract

The term "precision medicine" (also known as "personalized medicine") is broadly defined as the tailoring of medical treatment to the individual characteristics of each patient. This process entails classifying patients into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Subpopulations are defined through systematic analysis and classification of patients' genotypic and phenotypic characteristics.

Image findings are surrogates for phenotype manifestation of disease, and radiology reports are written descriptions of imaging phenotypes. Imaging phenotypes are often presented as classification, grading, or scoring systems that help assign patients to subpopulations for selecting treatment or assessing prognosis. The "spot sign score" that reflects the severity of bleeding in intracerebral hemorrhage is an example that has been used as an inclusion criterion in clinical trials.

The term "radiogenomics" is used to describe the study of linkage between a patient's genotype and imaging phenotype. When a patient's genotype is known, it often suggests a surveillance role for imaging to determine clinical occurrence, location, extent, and severity of the associated disease; for example, use of breast imaging for enhanced surveillance in women known to harbor the BRCA1 and BRCA2 genes.

Imaging is poised to play major roles in the age of precision medicine. The imaging community needs to learn new terminology and think in terms of how imaging phenotypes and imaging surveillance of patients with known genetic mutations can contribute to the concept.

Key Words: Precision medicine, radiogenomics, imaging phenotype, genotype, mutation

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In 2011, the National Research Council (NRC) of the National Academies in the United States published a white paper titled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" [1]. The NRC defined "precision medicine" as "… the tailoring of medical treatment to the individual characteristics of each patient." The NRC stated further that this entails "… the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment." The NRC prefers use of the term "precision medicine" rather than the older term "personalized medicine," because the latter implies the development or availability of unique treatments for each individual, which is not yet the case [1]. In his 2015 State of the Union address, President Obama announced a new initiative in the arena of precision medicine, with a commitment to request $215 million in the 2016 budget, for precision medicine initiatives.

Two overarching concepts from the NRC report [1] are of particular importance and relevance to the imaging community. First, the concept of precision medicine fundamentally entails better, more-specific, and precise separation of patients into the subgroups included in the NRC's definition. Second, the way to achieve this separation is through combining data about clinical phenotype with data about genotype or gene expression. Integrating information from new molecular or genomic methods with better clinical information developed through various means, including imaging, helps define more precise subpopulations. Acknowledgment of the importance of disease phenotypes in the NRC report

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counters a common misconception, fostered to some extent by President Obama, that precision medicine is based primarily on genetics. In fact, in current medical practice, disease phenotypes are far more important in the classification of disease than molecular or genotype data; to date, the system used to create the International Classification of Diseases (9th and 10th editions; ICD-9, ICD-10) is based almost entirely on clinical phenotype data [1].

PHENOTYPE

The term "phenotype" is used in medicine, and more generally in biology, to reference all the observable traits or characteristics of an organism. Originally, the concept and meaning of the term "phenotype" were restricted to grossly observable phenomena. In current use, the concept of phenotype and use of the term additionally encompass phenomena made observable through technologies that include imaging, laboratory testing, and various kinds of pathology studies. Disease phenotypes encompass all the observable characteristics related to a particular disease or condition.

In the context of precision medicine, grading, staging, and classification systems can be thought of as systems for defining subphenotypes of disease; that is, they are approaches to defining the subpopulations described by the NRC. Good grading, staging, and classification systems should segment patients into various prognostic categories as well as categories that may benefit from different treatments.

IMAGING AND DISEASE PHENOTYPES

Image findings serve as a proxy for phenotype manifestation of disease: They provide representation of the existence of abnormalities that can be identified, localized, enumerated, measured, and described, as discussed with D. Avrin, MD (April, 2011). Image findings, presented together in a radiology report, may be thought of as constituting a written description of the "imaging phenotype" of a disease or condition. In current usage, outside of radiology, the term "image finding" is replaced by "imaging biomarker," with a biomarker defined as any finding or parameter linked to the presence, severity, or behavior of a disease or condition [2,3].

Anatomic imaging dominated the first century of radiology, and the number of imaging biomarkers was restricted largely to the description of anatomic or morphologic parameters. Today, the imaging toolkit has expanded to include additional categories of molecular, metabolic, microenvironmental, and functional imaging biomarkers, providing a broad range of parameters on which to build imaging phenotypes.

Although never articulated explicitly, the fact is that radiologists are fundamentally in the business of creating imaging phenotypes through their systematic application and analysis of imaging studies, enumeration of findings, and application of grading, scoring, and classification systems linked to their findings. A simple but compelling example is the assessment of the bronchi using CT scanning. Radiologists routinely categorize bronchi as either normal or involved with various severities of bronchiectasis—cylindrical, varicose, or cystic—thereby readily separating patients into subpopulations, or subphenotypes, that have differing disease manifestations.

Clinical phenotypes, including imaging phenotypes, are pivotal in many aspects of medical practice and research. Apart from helping to group patients with the same or similar disease manifestations, they help in guiding therapy selection and assessing therapeutic response (response phenotypes). Separation of patients into subphenotype populations helps guide patient selection for clinical trials, and can help enrich populations of people who have similar biological characteristics, to facilitate the discovery of genetic mutations.

Clinical trials depend on matching patient characteristics to the treatment being studied. A daunting number of clinical trials have failed because patients were included without sufficient regard to phenotype. A clinical trial of factor VII, a clotting factor, in the treatment of intracerebral hemorrhage (ICH) failed to show a survival benefit because the complications of the drug in patients who are not actively bleeding counterbalanced the benefits of the drug in patients with active hemorrhage [4]. Several new trials for ICH treatment are underway; they use an imaging scoring system—the spot sign score—that identifies those patients who are actively bleeding, and the relative severity of the bleeding [5-7].

Without effective biomarkers for differentiating among patients who may benefit from various therapies, patients may be inappropriately included in clinical trials. A major challenge and opportunity in the age of precision medicine is for the imaging community to develop new and better systems for assigning patients to appropriate subgroups—subphenotypes—to improve the success of clinical trials. An "average" patient is not a definable concept, and the likelihood of clinical trial success increases with better classification of patients.

Assessing response to therapy in cancer is a common activity for radiologists. Four responses are possible, each