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DEEP PHENOTYPING

Treating the enigmatic "exceptional responders" as patients with undiagnosed diseases

EXCEPTIONAL RESPONDERS ARE PATIENTS WHO RESPOND TO THERAPIES IN WAYS THAT are both dramatically and unexpectedly positive but also statistically insignificant within the current context of most biopharmaceutical drug trials. Recent studies have demonstrated the genetic bases of some exceptional responders and unearthed secondary resistance mechanisms (*1*). These insights have stimulated great interest and a thirst for more knowledge. Organizations such as the U.S. National Cancer Institute are launching exceptional-programs to learn, from these unusual patients, how to improve therapies for traditional patients (*2*).

Occupying a similarly tiny but more unfortunate end of the statistical spectrum are adults and children who are afflicted with rare and undiagnosed diseases. Many rare diseases are genetic in origin, and the study of such disorders can yield insights into fundamental biology, which can, in turn, illuminate mechanisms that underlie more common diseases. This has proven to be true in next-generation sequencing studies of rare tumor samples, which have led to more intricate characterization of tumor pathologies, the establishment of new cancer classifications and subtypes, and new mechanistic insights.

The U.S. National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) defines rare and undiagnosed diseases as those that affect fewer than 200,000 individuals; diagnosis takes 1 to 5 years in 33% of cases studied thus far. In operation since 2008 and recently expanded to a full network of clinical and research sites nationwide, NIH's Undiagnosed Diseases Program (UDP) offers key insights into the management of exceptional responders in clinical trials regarding the efficiency and cost-effectiveness of focused and time-bound clinical assessment; the utility of agnostic whole-genome genetic studies, including patient pedigrees, to produce candidates for causal variants; the utility of rare patient populations in new disease discoveries; and the importance of deep phenotyping and careful review of the entire medical record of each patient (*3*). Each UDP patient is evaluated at the NIH clinical center in an intensive manner that is consolidated into a single 4- to 5-day visit. For patients with an apparent neurological phenotype, this week could include consultations in 10 areas of medical specialties, 20 various laboratory investigations, and 25 diagnostic procedures, some of which require sedation. All of these data are then considered in the context of the complete medical history of the patient, which is compiled in the 2 to 3 months prior to the clinical visit.

Would a cancer-specific, deep-phenotyping process similar to that of UDP patients be useful for exceptional responders? Considering the complexity and possible contributions of environmental and genetic factors, such a study could surely lead to insights or at least hypotheses that would enable a deeper understanding of such patients. This knowledge could then inform more targeted patient selection for future clinical trials.

Deep molecular phenotyping provides a richer understanding of population-wide, disease-course divergences, intratumor cellular heterogeneity, and histological variations and might pinpoint physiological alterations that can serve as therapeutic targets; at the very least, deep phenotyping would augment our knowledge about exceptional responders, even if it is premature to apply these findings to individual clinical cases.

The excellent work of the rare disease research community suggests a potential path forward. First, we need researchers who are willing and able to craft and execute experimental protocols that provide new information without compromising care or the quality of life of exceptional responders. Second, we must be proactive and transparent in establishing data-management and data-sharing platforms for the precious content that will result from these studies. Again, rare disease advocacy groups have demonstrated the feasibility of creating worldwide patient registries with informed consent that include genomic, clinical, and

environmental-exposure data, as well as a variety of self-reports. These data are made available to all qualified researchers.

Barriers to a deeper and more organized study of exceptional responders include cost, the avoidance of potential pain, risk, and unnecessary procedures the lack of available expertise, and the rigidity of the current regulatory framework. Also, because exceptional responders are scattered across institutional boundaries, both academic and commercial, the barriers to data sharing are well known to the rare disease community. Yet, prior experience and studies show that many patients, especially those who do well on a treatment regimen, are highly motivated and willing to help others with the same or similar diseases when informed consent is adequately described and nuanced for the specific study—even when the subjects are children (*4*). Moreover, the increasingly empowered rare disease community is becoming more vocal in its expectation of broad data-sharing practices.

In considering cost, oncology clinical trials are already quite expensive, having an average per patient cost of $59,000, which is significantly higher than the average per patient cost across all diseases of $36,500. (*5*). The unfortunate rarity of the exceptional responders does mean that the cost per patient will be considerably higher than the average, as is the case for patients in the UDP.

Existing expertise is a clear and present challenge. The focus of modern health care on time efficiency prohibits large-scale strategies that involve extending the time a clinician spends with each patient. Again, this is where clinical practice and biopharmaceutical research diverge. Programs such as the UDN are driven in part by the need to develop more capacity and expertise in deep phenotyping and genetic analysis. Outside the clinic, there are new tools and ontologies being developed that could further facilitate, educate, align, and even automate aspects of deep phenotyping. Indeed, the rare-diseases open-data and open-science community is one of the most prolific and transparent. Moreover, national projects, such as the Precision Medicine Initiative, projected to involve one million Americans, have at their starting point participant consent to broad data sharing for a variety of research purposes. Regulatory agencies are responding positively and are engaged in the conversation. At the same time, 660,000 people in North America die of cancer annually, and there is a growing recognition that we must rethink clinical research if we are to expedite faster and less-expensive access to new therapies for lethal diseases (*6*).

So what can we do, concretely and immediately, to apply what has worked well in the rare disease world to exceptional responders? To serve as the basis for further debate, we present a list of actionable desiderata for an Exceptional Responder Network (ERN):

- Enlist a national network of clinical sites that provides, at no additional cost, a series of molecular assays including somatic and germline genome sequencing. As in the UDN, this implies the existence of a set of centers that provide high-quality and current interpretations of these measurements. Participation will be contingent on agreement for data sharing.
- Create an exceptional responder registry open to all such patients across all trials whether led by companies or nonprofit or governmental organizations. The patient or their delegate will request that the patient's data be included in the registry. The ERN should have a coordinating center that uses a variety of manual and technological services to ensure that all relevant data—clinical and research—obtained from that patient are included in the registry.
- Data-sharing governance should be implemented by a steering committee with substantial patient and patient-advocate representation. At a minimum, all data should be made available to qualified researchers, including citizen scientists, who agree to appropriate secure data-handling procedures and oversight. Data should be released no more than 1 year after having been generated.

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