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The Patient-Scientist's Mandate

Sonia M. Vallabh, Ph.D.

Eight years ago, at the age of 27, I learned that I had inherited a fatal genetic mutation in the prion protein gene (*PRNP*). Pathogenic mutations in this gene cause genetic prion disease, a rare adult-onset neurodegenerative disease that is rapidly fatal once it strikes. The mutation I carry, which stole my mother's life when she was 52, makes me nearly certain to die of this disease if no preventive measure is developed.

In response, my husband, Eric Minikel, and I left our previous careers in law and transportation engineering to retrain in biomedicine. Starting in night classes and entry-level laboratory jobs, we earned our Ph.D.s in biomedical research from Harvard in the spring of 2019. In the process, we found our scientific home at the Broad Institute at MIT and Harvard, where we have now established our own laboratory focused on the development of therapies for prion disease.

There is a proud tradition of activated patients driving science. Fellow travelers of this path may be familiar with the kinds of questions we fielded from day one: whether it was wise to pursue genetic testing for a currently incurable disease; how we would weather the setbacks inherent in the drug-development process; whether it was appropriate for patients to work on their own disease. But we were fortunate to find mentors willing to fight alongside us, and together we forged a plan to tackle prion disease.

My goal is prevention: to preserve at-risk brains, including mine, in full health. Prion disease advances exceptionally swiftly: the average patient dies within 6 months after first having a symptom. Previous clinical trials have involved symptomatic patients and used a survival end point, accepting that many such patients are already profoundly debilitated at enrollment. But predictive genetic testing provides an opportunity, and arguably a mandate, to aim for a higher goal: preservation of full quality of life.

Because the onset of genetic prion disease is not preceded by an established molecular prodrome, testing drugs in healthy carriers will require a primary prevention strategy based on genetic risk. This realization has defined our priorities for the past 5 years,[1-3] leading us to focus on a drug target present in healthy people (normal prion protein, or PrP); a biomarker that can reflect drug activity absent a clinical phenotype (PrP in cerebrospinal fluid); tools for quantifying risk; appropriate recruitment infrastructure; the presymptomatic natural history of the disease; and proactive engagement with the Food and Drug Administration. As this list suggests, redefining the aims of drug development to encompass prevention leads to many new research goals. In the area of genetic prion disease, it took a patient-scientist to drive this shift. Perhaps there is something peculiarly clarifying about defining success by honestly answering the question "What would you want for your own brain?"

Since genetics provides an opportunity for prevention in only a subset of cases of prion disease, symptomatic-stage intervention will remain an important goal.

Prevention may, however, offer the best chance to establish the efficacy of targeted drugs, thus motivating earlier diagnosis of sporadic cases — a prerequisite for meaningful intervention.

In theory, there are many ways one could seek to reduce the amount of a single disease-causing protein in the brain. Our assessment of plausibly relevant approaches was guided by our bottom line: Which approach would face the smoothest path to a first-in-human trial in healthy carriers of prion disease mutations?

Guided by practicality, in 2014 we launched a cross-sector collaboration to develop PrP-lowering antisense oligonucleotides (ASOs).[2] The potential for these RNA-targeting oligonucleotides to modulate levels of a specific disease-causing protein in the human central nervous system was just being unlocked, as demonstrated by the progress since then of ASO drugs for other neurologic diseases.[4] These programs have allowed us to leverage established insights into basic properties of ASOs in the brain so that we can move efficiently. Five years on, this program is advancing toward the clinic.

This pace of progress is unusual and exciting, but we have paid a price for our pragmatism. The well-understood nature of ASOs — precisely our greatest asset — leads to charges of lack of novelty from manuscript and grant reviewers. We've found ways to continue our work, thanks to a supportive institutional home and a certain scrappiness born of our unwillingness to walk away. But whereas we remain determined to keep laboring uphill, the academic incentive structure may well have diverted other researchers toward more "fundable," more publishable, but less practical approaches. On the strength of the data so far, I believe that a PrP-lowering ASO may plausibly become the first effective therapeutic agent for prion disease, may prove able to delay onset in people at risk, and may reach the clinic within a few years. Would this work have happened, but for two scientists with life-or-death personal stakes in the outcome?

My patient-scientist lens highlights the unexpected power to be found in many kinds of information. On the research side, this information includes "negative results." For instance, up to now, data from our ongoing natural history study of genetic prion disease suggest that carriers are healthy, with no sign of pathology, for much of their lives,[1] and that, in contrast to Alzheimer's disease and other dementias, any presymptomatic molecular changes are unlikely to precede the onset of symptoms by more than a few years. This insight suggests that secondary prevention strategies based on prodromal pathologic changes may have limited application and encourages a focus on primary prevention. It also has immediate implications for carriers' understanding of their bodies and their risk. We owe it to this community to share such results and to recognize the value of data that support the null hypothesis.

On the patient side, an emerging task is to rally people who are at risk for prion disease. Currently, only roughly a quarter of those at known 50/50 risk pursue predictive genetic testing.[5] Many are counseled against seeking this information because an unlucky result is not actionable. I understand this argument, but there's more to actionability than meets the eye. To succeed in the clinic, we will need to rally supporters behind a counternarrative, one that honors the opportunity that carriers have to contribute to rewriting our collective future. This reframing will not persuade everyone at risk, but it will resonate with some. And, especially when dealing with a rare disease, every participant matters.

For me, the journey from patient to scientist continues to reaffirm that pursuing predictive genetic testing was the right choice for me and my family — a decision that continues to empower me in new ways as the years unfold. In 2017, Eric and I had a healthy, mutation-negative daughter through in vitro fertilization with preimplantation genetic diagnosis. Meanwhile, in the lab, we are racing to lay the groundwork for the day when clinicians can offer PrP-lowering therapeutics to healthy carriers of a genetic prion disease mutation, with the hope that I will be among them.

I still occasionally encounter the concern that there is a conflict of interest inherent in researching your own disease. But far from seeing a conflict of interest, I see an exquisite alignment of interests as I work with mentors and allies toward a trial in which I hope to enroll, testing a drug I hope to take, to prevent the disease that threatens my life.

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From the Broad Institute of MIT and Harvard, Cambridge, MA.

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