Risk and Return for the Clinician-Investigator

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In this case study, an early-career clinician-investigator discusses impending and future career issues in an interview with an established translational scientist, who then shares ideas about pursuing clinically informed research questions.

Case. I am Sarah Henrickson, a 32-year-old intern in the Boston Combined Residency Program in Pediatrics. I was born in Toronto, Ontario, where my parents worked as archaeologists at the Royal Ontario Museum. We moved to Washington, DC where I attended an academic sci- ence/research magnet program. As an undergraduate, I majored in biochemical sciences at Harvard University and engaged in research on the development of protein nanoparticles as DNA-sequencing and biosensing tools and the study of strategies used by virus to evade the immune system.

After college, I spent a year at the U.S. National Institutes of Health studying the geneti- cs of human leukemia and lymphoma before starting the M.D.-Ph.D. program at Harvard Medical School. My Ph.D. project involved the application of multiphoton microscopy to study factors that control the early phases of T cell activation. I worked as a teaching assistant throughout graduate school and loved teaching first year medical students about immunology. I was married in between undergraduate and graduate school, and my husband currently is a postdoctoral fellow at the Massachusetts Institute of Technology. I had my son (who is now almost 5 years old) as I was finishing my Ph.D., before completing my final 2 years of medical school. On the hospital wards during my 3rd and 4th years in the Harvard-MIT Health Sciences and Technology M.D.-Ph.D. program, I discovered a passion for pediatrics and plan to pursue fellowship training in allergy-immunology or hematol- ogy-oncology and then practice as a clinician-investigator. Now an intern in pediat-

rics, I plan to complete an integrated research program, so I will have dedicated blocks of time to pursue research (specifically, 6 months of research time in each of the last 2 years of residency). In addition to continuing my pur- suit of basic science questions in my graduate lab, I am currently working with a team of attend- ing physicians and principal investigators to study the underlying immunological defects that give rise to persistent skin infections in pediat- rics.

A GUIDE ON THE ROAD LESS TRAVELED

As the subject of this case study, my goal was to gain insight into how one prepares to be a successful clinician-investigator (1, 2) who translates observations in the clinic to investigations in the laboratory. Clinically inspired research can both enhance our under- standing of human disease and improve clinical medicine. As an M.D.-Ph.D. stu- dent, it was challenging to find role models who maintain both an active clinical and robust research presence, as many clinically trained professors choose instead to em- bark on basic science careers and leave the clinic entirely. During my residency, I have met more clinician-investigator role mod- els, and as I progress along my own career path, I actively seek out advice on how best to use my research training to address clinically relevant questions.

In this Commentary, I interview David Altshuler, M.D., Ph.D., a clinical endocrinol- ogist, human geneticist, and founding mem- ber of the Broad Institute in Cambridge, MA, USA. As I proceed toward my planned future as a clinician-investigator (1, 2), my goals for the interview were to gain advice about (i) what additional postdoctoral research ex- perience I may need; (ii) how to choose appro- priate research questions; (iii) whether I should use my time as a resident to explore a new field of research; and (iv) skills required to orchestrate a laboratory and medical team. Finally, I sought some expert strategies for prioritizing the diverse responsibilities of a demanding, multifaceted career path and for ensuring that I maintain excellence in both the clinical and research arenas.

Dr. Altshuler, who trained at the same in- stitution as I did but nearly 15 years earlier, offered some “just-in-time mentoring.” Our discussions focused on career dilemmas that my peers and I face at the residency stage, such as how patients and previous research training might influence the direction of one’s research and the effects of long training times on one’s life and work.

Fig. 1. Embracing risk opens new vistas. “To be on a wire is life. The rest is waiting.” [Joe Gideon, in the film All That Jazz (1979); generally attributed to circus daredevil Karl Wallenda]
**PATIENT CONTACT INFORMS RESEARCH QUESTIONS**

**Q. Sarah:** During their training, some medical students, residents, and fellows dream of both treating patients and engaging in laboratory research that changes the face of medicine. But beyond gaining a general perspective on the importance of human disease research, it often isn’t clear how clinical practice can inform laboratory research directly. *Why should someone who wants to engage in biomedical research pursue an M.D. degree rather than proceeding directly (or exclusively) to a Ph.D. program?*

**A. David:** For me, there were at least three good reasons. First, I just wanted to be a doctor—to take care of sick people, to better understand the human experience. I wouldn’t give up that experience for anything. Second, taking care of patients proved to be a source of lasting motivation. Before clinical training I struggled a bit to find a source of motivation more lasting (and perhaps more justifiable) than simply career success or satisfying my own intellectual curiosity. Medicine relieved of that angst—it became very concrete that there are real people out there suffering and that more knowledge is needed to develop improved ways to help them.

Third, clinical training profoundly affected the direction of my research. From taking care of patients every day and talking with their family members, I became fascinated by the many patients I met with type 2 diabetes who had family members with the same disease. I remember it like it was yesterday a night in the Cardiac Care Unit when a young man came in with a heart attack before the age of 40, and his wife explaining that his brothers had both had heart attacks at a young age. And yet, despite these being among the most common and important diseases in medicine, no one had explained this familial observation at a molecular and mechanistic level. Having trained in genetics as an approach for dissecting biological processes, I wondered if genetic mapping could be used to find the underlying causes of type 2 diabetes and heart attack.

This wasn’t a convenient match of a research question and a clinical need—in some ways, it was very inconvenient, because there weren’t any proven methods for identifying the genetic causes of complex, common diseases. Rather, this was a medically important research question that I found deeply interesting and might be productively studied with coming advances in genetics and genomics.

Sarah: Yes, I see what you’re saying. As a 4th year medical student rotating through dermatology, allergy, and immunology clinics I saw patients with multiple simultaneous, severe, viral skin infections, many whose parents had similar issues when they were children. Coming from an immunology background, I wondered if these families carried a genetic defect either in their skin or in immune system components that protect the skin from infection. These experiences on the wards are inspiring me to study systems-level disruptions of the immune response that form the basis of human disease.

David: Exactly. It is important to realize that, in medicine, the universe of what we don’t know is much larger than that of what we do know. If you open your eyes in the clinic, you’ll find an endless number of patients whose disease process is poorly understood. I find this knowledge gap incredibly motivating. As long as there are these major gaps in our understanding of human disease, we are going to be grappling in the dark in our efforts to devise new ways to help patients.

In my mind, it is also critical to remain true to the conviction that, if your goal is to understand and possibly have an impact on human disease, you have to connect your research back to the patient’s experience. As powerful as cell and animal models are to understanding basic biological mechanisms, there is a gulf between that model and the patient in front of you. Seeing patient after patient with disease made me realize that the typically studied models capture a tiny slice of the variation we see in human disease. If we rely solely on existing models, we run the risk of missing many of the biological pathways that are important to human disease and that can be exploited to develop therapies that will work in patients (Fig. 1).

Q. Sarah: So if clinical experiences drive laboratory investigations, *why should someone who wants to engage in patient-driven biomedical research pursue a Ph.D. or M.D.-Ph.D. degree?*

A. David: Graduate training teaches about rigor and the range of approaches that can be deployed in the investigation of a research question. Just as a doctor needs to know how to do a physical and interpret lab tests, a scientist needs to know about experimental design, analysis, and interpretation. In addition, being facile with a variety of research tools lowers the activation energy barrier that can prevent a researcher from diving in and performing the combination of experiments needed to answer a scientific question about human biology.

There is also the issue of standards of proof: Scientists frequently work for years in the lab to prove one point. It’s important to know in the starkest possible terms the difference between data that are suggestive and proof. But in medicine, the premium isn’t on proving something beyond a reasonable doubt—it’s often on making a good decision under time pressure and without all the facts you might like to know.

So these two types of training provide a clinician-scientist different perspectives—formal research training instills, most importantly, a high bar for believing that something is true, while clinical training provides the ability to make a tough decision (when needed) on the basis of imperfect information.

**EMBRACING RISK**

**Q. Sarah:** Because we haven’t done many (if any) clinical rotations before we select our Ph.D. laboratories, M.D.-Ph.D. students often choose their graduate research projects on the basis of their prior research experiences or course work. Then, once you get to the hospital wards, it can be unclear how your research relates to clinical observations, and it can be difficult to imagine how to move forward as a clinician-investigator. I was lucky: As I considered my data while in the clinic, I came to see a link between vaccine science and my graduate work in immunology. As I choose new research questions, *how large a role do you think one’s research training should play in decisions about future fields of study?*

A. David: In my mind, the point of research training is to teach you to think like a scientist and how to design and interpret experiments. You should be able to take those skills and apply them to the study of any biological problem. I think you could do research in immunology for your Ph.D. thesis and then go work in any subfield of biomedicine as a postdoctoral fellow.

Q. Sarah: But when students and fellows have made choices early in their training that yielded interesting research questions and a degree of expertise in a given field of study, it can be hard to leave that original field behind for a new focus spurred by experiences in clinical training. *What advice would you give an early-career clinician-investigator who is considering changing fields in order to pursue a new clinically inspired question?*

A. David: I would advise you not to limit yourself—not to differentiate your research...
direction prematurely. If one of the values of clinical training is exposure to a wide range of unsolved medical problems, then it would be a shame to have blinders on that limit your willingness to study the question you might encounter. Rather, I’d suggest that you see your training as a means of providing a generic tool kit that you can apply to the most important unanswered question that you observe in clinical practice or in a research lab.

I think people worry too much about making good on a previous investment of time and effort. What’s wrong with changing your focus as you gain information? You’re a smart, able person, and you should pursue whatever research question is most compelling to you and that you think will be most productive in advancing human health. There is no reason that your research focus should be limited to your previous sweet spot.

Q. Sarah: In many residency programs, one is channeled into an exclusively clinical 3- to 5-year block of time. At the end of that period, one can either step right back into one’s previous area of scientific expertise and try to regain those connections, or one can try a new field. Is it not tempting to go with what you had previously loved, studied, and, to a limited degree, mastered?

A. David: If you love it, then sure. But I’m just saying that you should have an open mind.

Certainly, this was my experience. I did my Ph.D. in developmental cell biology; the lab didn’t do genetics—that is, we didn’t breed things, we didn’t study inheritance of genes—and yet, after clinical training, I went on to become a human geneticist. I knew absolutely nothing about human genetics, population genetics, or genomics. I didn’t even realize how little I knew! But once I dove in, I realized that I could learn what I needed to know, because my Ph.D. training and laboratory research experience gave me an approach, a way of thinking.

Q. Sarah: How do you recommend that one increase his or her tolerance for risk?

A. David: I think that risk aversion is one of the greatest risks to young clinician-investigators. In watching a lot of scientists over time, I have come to believe that to make truly important advances in scientific research, one has no choice but to take risky research paths with uncertain outcomes. Because the only way you can know a path will be productive—that there isn’t any risk—is if the answer is already known or obvious. If the research problem is truly unsolved, then there is risk that you won’t solve it either, or that what you find will be difficult to understand or follow up.

One problem is that M.D.-Ph.D. candidates and early-career clinician-investigators are typically people who have been very successful in their young lives and who worry about failing to live up to that early success. Taking the kinds of risks that are necessary to make truly new discoveries is a gut check for many people. In my view, in order to try something completely new, a person must be willing to fail; that doesn’t come easily to accomplished young people who—having devoted so many years of their lives to training and to establishing independent research careers—feel the need to diminish their risk of failure. People become conservative in their decision-making in order to minimize risk, and I think that is a strategic error, because it limits you to problems for which someone else has already reached the point where the outcome is predictable.

So, paradoxically, I would argue that it can be a bigger risk to choose a research path that seems certain than to choose one that may be more risky, because the most important research questions are, by definition, the ones we don’t understand yet. This can be hard to comprehend, because when you look at scientists who have been successful, it can appear in retrospect as if the approaches they chose were obvious at the time. But this is seldom the case prospectively.

Back in 1996, when I was deciding to join a lab that was studying the human genetics of complex common diseases, many of my mentors advised me that working on complex-trait genetics was a terrible idea. They said that we were unlikely to make progress, because progress had certainly been slow to date, and that if we did, it might not be interesting. Later, when I decided to set up half of my lab at a genome center and half at a hospital, I was told that such an approach was very risky, because at that time, there was no comparable model with a proven track record. Some people weren’t happy about my decision, because it wasn’t in accord with their view of how science should be organized or how I should spend my time. So, doing things differently wasn’t risk free.

You might justifiably ask why I did it, given these risks. I don’t really know, other than that I really believed in the research we were doing and the model we had come up with for doing it. But if I had minimized risk at the beginning of my independent career, I wouldn’t have had the remarkable opportunities that I’ve enjoyed over the last 15 years.

Q. Sarah: But when trainees assess successful senior scientists, how can we distinguish between the possibility that junior clinician-scientists who took big risks failed miserably and left academic science versus the possibility that successful researchers generally make the risk-taking phenotype—that they asked the questions other scientists weren’t asking or asked the questions in a new way?

A. David: This is truly the $64,000 question and a very hard one to answer. Ultimately, it’s about making good decisions. If the problem is too hard—if you don’t yet know enough or if the methods needed can’t be developed—then it’s a bad choice, because you won’t make progress. But, if the answers are too near at hand or unlikely to inform an important unsolved question, then you can be doomed as well. You’ve got to find that balance of risk and benefit—the willingness to take risks to do something important, but not irresponsible or uninformed risks.

Sarah: I hadn’t thought about risk that way before, but what you say makes a lot of sense.

David: If you’re not willing to do something that is hard, you are almost guaranteed that what you do won’t matter. And embracing risk can be difficult for clinicians, because the alternative pursued by many of their peers—clinical practice—is a relatively secure life. But being a scientist is not secure by definition; even if you are an established researcher, even if you have tenure, you still have to explore new problems that you don’t know you can solve, to send your papers and grants for peer review, to face regular rejection. You have to embrace constant uncertainty if you want a life in the lab.

LONG AND VARIED ROAD

Q. Sarah: You’ve convinced me that one should view graduate-level research as a time in which one learns to be a biomedical scientist in general. And the willingness—courage—to jump in and use my training as a scientist, without simply defining myself as an immunologist or an imaging scientist, for example, clears a path for allowing clinical insights to further motivate my (and my future trainees’) research—and strengthens my underlying passion for understanding the fundamental questions in immunology, all while serving patients. Does the same advice apply later on in one’s career, after one has established a successful research lab?

A. David: Certainly, you want to stick with a problem long enough to make an impact and to leverage your investments.
in learning and in generating reagents and knowledge. But, in a scientific career, you have to reinvent yourself every 10 to 15 years. The scientists I admire most have all done this.

In my case, I’ve now spent 15 years trying to understand human disease by using genetic and genomic methods. At this point, I can see that many of the questions that inspired me to enter this field are moving toward answers. And having developed methods where we can pinpoint human disease genes and biological pathways, the most important questions shift downstream. So I’m taking my lab in a different direction, one that I hope will enable us to make new discoveries about human biology and ultimately build a foundation for the discovery of novel approaches to therapy. Going forward, it’s clear to me that the rate-limiting step will be to decipher, for a given set of genes that contribute to a given disease, the functions of disease-related gene products and their contributions to human physiology and pathophysiology.

Note that this move is risky. My lab is good at human genetics and, yet, has much less of a track record in the functional study of gene products. And most of the disease-associated genes we’ve identified have not been studied previously, and so we lack basic knowledge about the molecular functions of the products of these genes as well as preexisting assays with which to study these functions. So, we have to create all that. It’s risky. But it’s what we need to do if we are going to deliver on the investment made to date in human disease genetics, so what choice do we have?

Q. Sarah: A clinician-investigator must complete additional training before he or she applies for a first faculty position and, being older, often has more responsibilities than do many of his or her peers. How have you balanced a risky career as a clinician-investigator with having a family?

A. David: This is definitely one of the hardest things about the M.D.-Ph.D. career path—the extended training that takes you well into your 30s runs up against the timing of having a family. If you choose to do both of these at the same time, you really need a strong support network—your life partner, family and friends, childcare all have to be in place. You can’t do it alone, no matter how hard you work. You have to be comfortable relying on other people—and you have to thank them and let them know how much you appreciate their efforts!

Ultimately, this is the only life you have, and if you want to do work that requires intensity and dedication and have a family, then you have to be willing to compromise in some ways. It may be where you live, to minimize travel time between home and work; it may be financial, in that you spend more on housing and childcare then you otherwise would; it may be giving up something you love, or having to say no to an opportunity you would like to accept. But something has to give—you can’t be all things to all people. You have to know what your priorities are and be willing to defend them in face of outside pressures, and to feel comfortable focusing on what you feel is truly most important.

LEARNING ANNEX

It was illuminating to discuss career issues with someone who has walked a similar path but has not been involved thus far in my ongoing series of education and training decisions. I see in myself the struggle David described: I’m constantly working to balance my excitement about investigating cutting-edge biomedical research questions and serving patients within the practical confines of limited time and resources.

I was encouraged and motivated by talking through the challenges and opportunities of merging both careers into a unified whole—that of the clinician-investigator—with someone who took a similar training path and who continues to use clinical observations to drive his research. As a result of this conversation, I will strive to be freer in my choice of questions and methodology when pursuing scientific answers. Further, I was strengthened in my desire to be a true clinician-investigator by allowing unmet medical needs and clinical insights inspire my research. At the same time, I am dedicated to the scientific approaches and techniques that I learned in my training as a basic biomedical researcher—and the kinds of intricate investigations into physiological mechanisms that this “toolbox” makes possible. Thus, I plan to apply the perspective and rigor I learned from engaging in basic research during my Ph.D. training to clinically relevant questions about human pathophysiology that pave the way for improvements in clinical medicine and a better understanding of the underlying immunological mechanisms.

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