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SEPSIS NEEDS DIAGNOSTIC START-UPS. A LOT OF THEM

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A university-based investigator discovering a new way to diagnose or manage septic patients must reconcile two nearly incompatible realities. One is this: a diagnostic test that helps her patients is one that can be sold in sufficient quantity at a sufficient price to allow its maker to sustain its business operations and payroll, recoup its cost of development, fund new research to extend the tool's refinement, and *from the outset* attract sufficient investment—likely tens of millions of dollars—to bring it from the bench to the bedside. For her, these hurdles are at best unfamiliar and are at worst so daunting in their scope or even off-putting in their financial focus as to dissuade her from even bothering with translation. Many of you reading this first paragraph may feel the same way.

The other reality is why she pursued her career in the first place, summed up by her third grader proudly declaring on the first day of school: My mom does science that saves really sick people's lives.

Too many die of sepsis. Those charged with preventing this have been armed with too few tools for too long. The tests at their disposal are blunt. The discrepancy between the diagnostic tools available for sepsis and those for cancer—the hardcopy of the American Joint Committee on Cancer's Eighth Edition Cancer Staging Manual is over 1,000 pages long—is as wide today as it was when many of us began studying sepsis ages ago. Decades of experience confirm that publication is not enough, and research grants and endowments are not enough. No one is coming to carry our discoveries over the finish line. If we want better tools for patients, we need to do more than just explore their possibility. We need to launch more companies.

In 2018, I co-led a working group at the National Institute of General Medical Sciences tasked with evaluating and reimagining that institute's approach to eradicating sepsis (1). The team strongly recommended that the National Institute of General Medical Sciences focus on translational knowledge to be gained in the clinic. A major effort should be to create new tools and methods that diagnose and endotype patients, allowing more precise use of available treatments. One can imagine that some tools (e.g., easily calculated clinical scoring systems) might gain adoption in the absence of a company to bring them to fruition. However, most sophisticated data analytical methods, monitoring algorithms, and biological assays need years-long development, clinical validation, regulatory approval, manufacturing and product support, and a means of getting the final tools to caregivers (i.e., a sales strategy). In this light, how can the National Institute of General Medical Sciences working group's call to build new tools be viewed as anything but a call to start-up?

It is a difficult charge. The time and money needed to bring a new tool to the clinic are formidable. Figure 1 shows the investment trajectories, from the time of first investment, of all oncology or sepsis start-ups focused on diagnosis, staging, and endotyping between 2000 and 2021 for which public records are available (2). Investments are deployed in much the same way as grants—to support salaries, experiments, and operating and sales and marketing expenses—as well as gaining regulatory approval. Before their products becoming widely available for purchase, these companies routinely require tens of millions of dollars.

Two things in these data strike me. First, over the past 20 years, oncology diagnostic start-ups have outnumbered sepsis diagnostic start-ups by more than 5 to 1. Second, the financial path of development for new companies in these two fields is remarkably similar and marked by several early years of exponentially growing capital needs that far exceed the capacity of a usual research grant. Starting a diagnostic company is an expensive proposition, but I for one am heartened by the capacity of sepsis start-ups to grow at the same pace as their more numerous and often better-hyped oncologic kin.

What has become of these sepsis start-ups? Of the 27 for which public information is available, eight companies have brought products to market; four of these have subsequently been acquired by larger companies. Twelve remain in preclinical development, four have pivoted to a clinical indication other than sepsis, and three have failed.

It is useful to further underscore the disparity between what is funded by small business research grants and what is provided by private investment. Figure 2 summarizes funding activity between 2000 and 2021 through Small Business Innovation Research and Small Business Technology Transfer grants. Also shown are equity investments in the form of 'Friends and Family,' angel, and early-stage venture capital and venture debt.

First, each year, only a modest number of companies are supported to develop new technology in this space—usually fewer than 10 receive grant funding or complete a new round of investment. Note that neither the federal government nor investors place an effective ceiling on what they will invest in this space. Investors can follow new opportunities freely, and federal agency leadership has wide latitude in directing its SBIR dollars. I believe the low level of activity likely points to market entry, more so than available capital, as being the limiting step.

Second, over time and as expected, many more companies receive SBIR funding than equity investment. Between 2000 and 2021, a search of federal government and investment records

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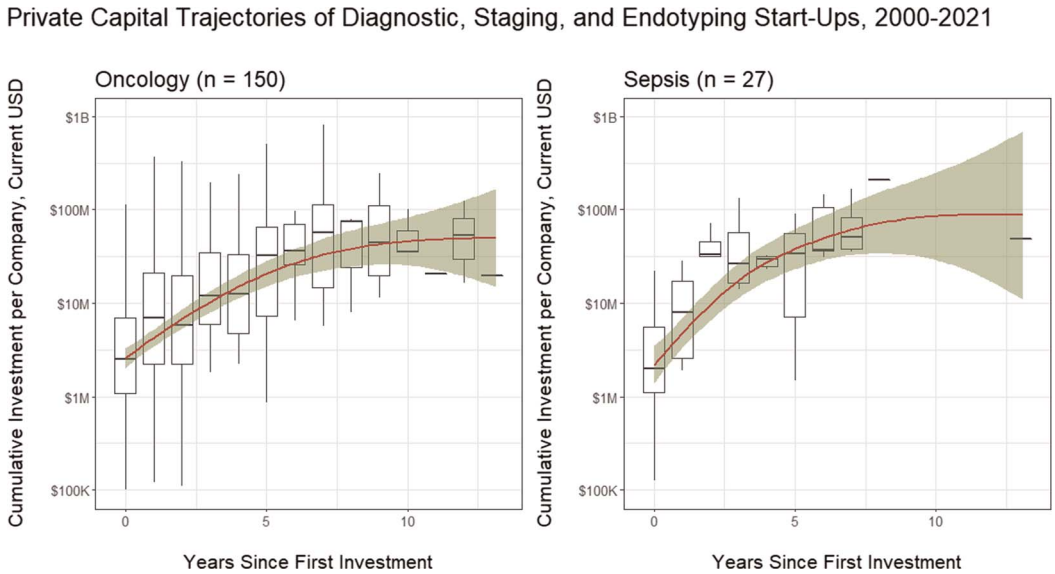

FIG. 1. **Financing histories of start-ups developing technologies for use in diagnosis, staging, and endotyping for cancer (left) and sepsis (right) since 2000**. Trajectories indicate accumulated private investment within individual start-ups, excluding grants, beginning with the first publicly acknowledged capitalizing event. Sepsis companies raise similar levels of investment at a rate similar to oncology start-ups—both experience exponential increases in capital requirements within a year of onset that plateau by years 5 to 7. The important difference between the two disciplines is the number of launched companies. Five times as many oncology diagnostic and staging start-ups raised venture capital over the past 20 years relative to sepsis start-ups. Box plots are shown as 2.5th, 25th, 50th, 75th, and 97.5th percentiles. Trend line represents mean capital raised over time with 95% confidence band for the mean. Note logarithmic vertical axis. See text for details.

identified 97 start-ups with SBIR funding, whereas only 27 received venture backing. Small Business Innovation Research awards are short-term endeavors that in most instances support less than 1 year of effort while venture investments are typically extended, serially tranched undertakings that engage a company for years.

Third, although distributed among fewer companies, the amount of private capital flowing into sepsis diagnostic and endotyping start-ups dwarfs the funding injected by the SBIR/STTR mechanism at the NIH and FDA. Although raising investment is difficult, a scientist considering launching a company should not dwell on concerns about availability of funds as a reason not to move ahead. Even more importantly, researchers imagining new ways of caring for patients must not let familiar financial constraints of academic funding—things such as modular grant budgets and maximum allowable costs—limit the scale and scope of their vision for what is possible.

To underscore the clinical (and hence commercial) promise of recent sepsis research, I have tabulated publications appearing in Shock over the past 18 months with potential near-term value (Fig. 3). Fifty reports warrant attention, nearly 3 per month. Note that these reports all describe research which might be deployed almost immediately in the form of a start-up. Not shown here is a similar analysis of the basic science work that might yield new opportunities in the mid- to latter-part of this decade.

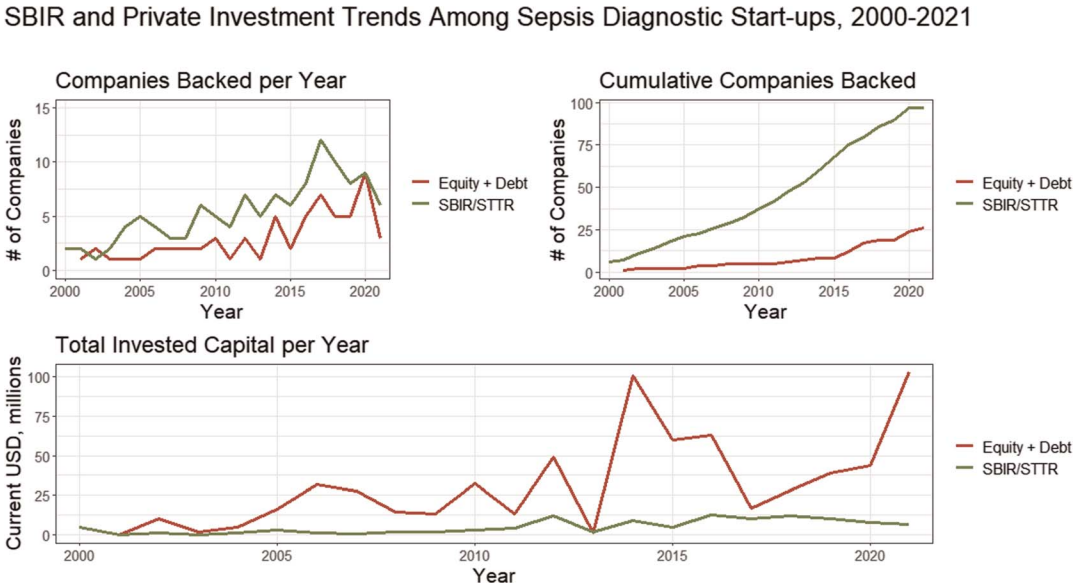

FIG. 2. **Twenty-year SBIR/STTR and private investment trends in sepsis diagnostic and endotyping start-ups**. Twenty years of CrunchBase and NIH RePORTER records were reviewed for the number of companies that self-reported a focus on sepsis diagnosis or endotyping and the amount of capital those companies received each year. While SBIR grants are awarded to many more start-ups than will receive venture investment, the size of private investments is often 10-fold or greater than small business grants. See text for details. SBIR, Small Business Innovation Research; STTR, Small Business Technology Transfer.

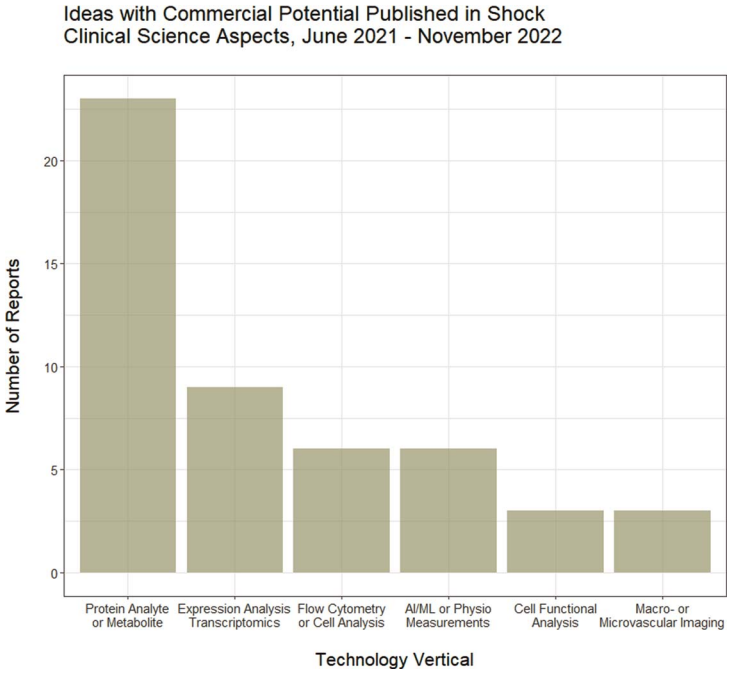

FIG. 3. **Frequency of reports published in the Clinical Science Aspects of the *Shock* journal in the past 18 months that suggest a path to commercialization.** AI/ML or Physio, artificial intelligence/machine learning or physiological signal monitoring and analysis.

How then should our scientist proceed? At a strategic level, she must address a fundamental career question: To what degree is she the shepherd of her ideas and discoveries and to what degree is she the shepherd of a laboratory that generates and studies ideas? I ask this question provocatively, as I have previously, because of its importance (3). One's place on this continuum should be actively chosen and revisited at least every few years. Full commitment to bringing an idea to the clinic implies at some point she leaves her laboratory to further move the idea closer to clinical reality. This can be professionally both disruptive and rewarding. Full commitment to her laboratory affords her the capacity to continue to create, but risks important ideas being dropped because no one steps forward to continue the ideas' applied development. Importantly, she cannot approach this career question without explicitly considering her own and perhaps her family's capacity to take on new risks and new opportunities. Furthermore, in the current academic and macroeconomic climate, she must also contemplate dispassionately the relative security and future opportunities, or lack thereof, provided by her status quo.

Her philosophy on the degree to which she will leave her previous role to champion her idea may materially impact the fate of that idea. It is notoriously difficult to estimate rates of success for university-derived biomedical inventions. There are long time lags between invention and ultimate commercial outcome—often a decade or more. "Success" is not easily defined. Significantly, it may not be in universities' interest to share some of these details either within the university or to outsiders.

The most common (and comfortable) choice for many inventors—asking their technology transfer team to identify an existing company interested in licensing the invention—may be the least likely to succeed. Stanford University recently published a 50-year review of its technology transfer experience (4). Arguably, this institution has as much experience with this effort as any organization in the world. After analyzing the fate of 4,512 inventions from their faculty, two important conclusions arose. First, the university recoups its internal administrative and patenting costs in only 20% of inventions. Second, and consistent with my experience, the strongest predictor of an invention leading to meaningful commercial revenue is that invention being licensed to the faculty member who invented it. Our inventor's passion and vision may be difficult, if not impossible, to outsource.

Tactically, there are several practices that I believe can increase the likelihood of new diagnostic and endotyping tool making it into patient care. Most involve our inventor expanding her network to help with matters outside of her research experience:

- *Regularly engage with members of her Office of Technology Transfer.* These experts are important resources when scientists believe an idea may have a shot at becoming a clinical reality. They are very familiar with intellectual property and university-based licensing, which companies may be interested in licensing an idea, and what institutional and local resources are available for launching one's own company. However, it is important for her to understand who these colleagues are not: they are neither customers nor users of her technology, they are not the team that will further develop her idea, and they are not investors. They may have no firsthand start-up experience as founders. They represent a university and its financial interests. To the extent those interests align with an inventor's, they are a valuable resource. To an inventor launching her own company, this dynamic is different. Technology transfer offices are a party with which the founder will need to drive negotiation to secure intellectual property with terms most favorable to her company. In both cases, a good working relationship is an excellent investment.
- *Bring clinical laboratory or health system information technology expertise onto the team.* Colleagues directly involved in patient care are an essential source of clinical understanding. However, like technology transfer officers, clinicians may have little insight into the details of a technology's path to commercialization and will have only a limited role in what needs to happen next. For the most part, clinicians do not make the financial and implementation decisions that make a tool available within a health system. Instead, clinical laboratory leaders can be a key but often overlooked asset during the development of

a new diagnostic method. Clinical laboratory directors have deep expertise in the method-validating and regulatory issues around FDA-approved and laboratory-derived tests. Health system information technology leaders understand what is involved in bringing software into their production environment and the interoperability and regulatory (e.g., Health Insurance Portability and Accountability Act) hurdles that software must clear. Both specialists can provide insight into how technologies will be purchased and how they will, and at what price point, be reimbursed. Oftentimes they may bring knowledge of existing and emerging competitive technologies. Research teams thinking of migrating a technology from what is possible into what is practical will benefit from these conversations. In my opinion, the sooner these real-world experts are engaged, and in a substantive way, the better.

- *Identify outside legal counsel.* If our scientist is thinking about launching her own start-up, an experienced start-up attorney is likely the first collaborator she will need to identify and retain. Note that this is *not* a patent specialist. Rather, it is an attorney with the experience to draft practical articles of incorporation, oversee the creation and negotiation of the company's first contractual documents (consulting and hiring agreements, facility leases, etc.), and coordinate the earliest private investments. Critically, this person will have experience negotiating intellectual property license agreements with universities. Even if our scientist is not interested in pursuing a start-up on her own, outside legal counsel can be a very helpful way for her to understand, and keep track of, activities her university is pursuing relevant to her invention. I contend that in no case should she rely solely on legal counsel provided by the university or directly university-affiliated incubator. There is an unavoidable conflict of interest in these situations, and it is not in her favor.
- *Begin conversations and schedule regular check-ins with potential investors.* Developing new diagnostic and endotyping tools to profitability is expensive. It cannot be accomplished with grants. Business development plans that culminate in receiving a federal grant are not development plans at all. Although new models of financing are likely to appear in the postpandemic early-stage investment world, capital in exchange for company equity is still the most likely path for start-ups in this field. Regardless of her intent to join a company, our scientist should begin making contacts with early-stage investors. These could include "friends and family," angel investors and angel investing groups with expertise (e.g., New York Angels, Life Science Angels), and the growing number of seed-stage "micro-VCs." Working together, these investors can invest the first million dollars or more in the right opportunity. And more so than with more mature start-ups for which investment decisions are made on company progress and expectations of the market opportunity, early-stage investing is a very personal activity. Angel and seed-stage investors rightly observe that they are investing in founders as much as a technical idea. Scientists seeking to position their idea for investment are also positioning themselves as either a founder or an essential resource in the company that will develop their idea. Although pitch competitions and polished slide decks receive oversized attention, it is the recurring one-on-one conversations that generate enthusiasm and trust among investors and ultimately will win the day.

Early conversations with investors will also familiarize the scientist with what will necessarily be given up in exchange for outside investment. A useful rule-of-thumb is that most traditional investment stages (e.g., Seed, Series A, Series B, etc.) will each result in the company selling one-quarter to one-third of its stock to investors. Concomitantly, a founder's power to guide decision-making in the company will ebb as investors recruit progressively more experienced members into the leadership team. Dialog with potential future investors will help her understand what will happen during the natural maturation of her idea.

Although perhaps the least familiar and most anxiety-inducing, for a nascent entrepreneur building a network of early investors should be viewed in the same way as sitting down with NIH program officers at a national conference. She may be surprised at the reciprocity of the relationship and may be brought in as a trusted advisor to help an investor evaluate other new technologies.

The COVID-19 pandemic has provided us with a profound reminder of the impact of unleashed systemic inflammation, but also with a moment to think clearly about our careers, our personal and professional goals, and our prior and future paths. The need for and opportunities provided by start-ups in sepsis have never been greater. The breadth and depth of scientific talent to launch disease-eradicating technologies have never been more plentiful. Capital is at hand. Surely this is a moment to dream a dream and seize the day.

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