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Developing In Vitro Diagnostics for Commercialization and Clinical Implementation

Ping Wang

Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania

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Summary

- Even though in vitro diagnostics (IVDs) account for only 3% of healthcare spending, they generate results that drive 70% of healthcare decisions by providing vital insights into patient health.
- Development and implementation of IVDs should provide value not only within the diagnostic lab but also downstream in the clinical care pathway, by improving clinical outcomes and decreasing costs.
- This can be achieved by developing assays for new clinical biomarkers and/or with new analytical technologies that address unmet clinical needs.
- Academic entrepreneurs can either serve as technology inventors or subject matter experts and partner with major IVD companies to develop assays or platforms, or partner with startup companies to secure grants/venture capital funding to support the development, clinical validation, and regulatory approval of the inventions.
- Following regulatory approval, effective clinical implementation and adoption requires analytical performance and user experience suitable for clinical needs, reasonable placement of the technology within the clinical care pathway, effective user engagement and support, and positive health economics. There are opportunities for academics to engage and contribute to all of the above aspects.

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Developing In Vitro Diagnostics for Commercialization and Clinical Implementation

Ping Wang, PhD, DABCC, FAACC¹



Topic Relevance by Timeline

Summary

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¹ Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania

Introduction

In vitro diagnostics (IVDs) include assays and/or devices used to test human tissues or body fluids outside of the body, and to generate results for clinical decision-making in disease prevention, diagnosis, prognosis, or treatment. Although IVD testing costs account for only ~3% of healthcare spending, the results drive ~70% of healthcare decisions, thereby offering a lot of value downstream in the care pathway (Rohr et al.). The development of novel IVDs should follow the same principle, with the goal of generating value not only in diagnostic testing itself but also in the downstream care pathway (The Lewin Group, Inc.). Tests for new clinical biomarkers or with new analytical technologies are developed to allow more rapid, more sensitive, and more specific diagnosis of diseases, as well as higher efficiency in care coordination, which leads to improved patient outcomes and lower care costs. These are the driving forces behind IVD development, with a market compound annual growth rate estimated at 5.2%, to reach a market value of \$87.93 billion by 2023 (ReportsnReports). Growth is driven by an increase in chronic diseases, emerging infectious diseases, precision medicine, automation, point-of-care testing, and emerging economies (Glorikian).

Regulation

The development and clinical practice of IVDs are governed by two main regulatory agencies in the United States. IVD developers submit applications to the Food and Drug Administration (FDA) for either PMA or 510(K) approval to market their products as medical devices (see the chapter “FDA Device Regulation: 510(k), PMA”). The FDA categorizes each device as waived, moderately complex, or highly complex, depending on the complexity level, including: knowledge to perform; training and experience required; reagents and materials preparation; characteristics of operational steps; calibration, quality control, proficiency testing materials; system troubleshooting and maintenance; and results interpretation and judgment. The supervising and performing personnel requirements and the quality control and validation requirements differ among these categories. Laboratory and personnel accreditation, certification, compliance, and reimbursement fall under the Centers for Medicare and Medicaid Services (CMS), which uses the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations as the federal standards for all clinical laboratories. The Centers for Disease Control and Prevention (CDC) also supports clinical laboratory testing by providing scientific and technical advice and resources.

Developing IVDs for Commercialization

IVDs may be used in several different settings (CLIA-certified clinical laboratories, physician offices, pharmacies, or homes). At this time, clinical implementation of novel IVDs may occur through two pathways: lab-developed tests (LDTs) or FDA-approved tests. The LDT pathway limits the practice of the test to the clinical laboratory that develops it. The FDA has historically exercised enforcement discretion on LDTs, but has indicated in recent years its intent to regulate

this category. Since the regulatory outlook of LDTs is not well defined at this stage, the rest of the chapter focuses on the pathway with the goal of FDA approval and wide clinical implementation.

There are many different ways academic entrepreneurs may lead or participate in IVD development. In one scenario, the academic entrepreneur may license a novel biomarker and/or associated assay, or license an assay platform from the research lab to a major IVD company for commercialization. The chemistry and engineering expertise of the IVD company may be leveraged to further develop the assay into formats more suitable for high-throughput testing, in order to achieve maximal distribution and impact. The medical affairs resources of an IVD company may also be leveraged to further demonstrate the clinical performance of the biomarker assay in disease detection or prognosis—comparable or superior to existing biomarker assays—in large patient populations. The IVD company takes the product through final regulatory approval. In another variation, the academic clinician may contribute clinical expertise and resources to clinical validation of the assay, which may be crucial for IVD companies to submit for regulatory agency approval, or for startup companies to obtain funding for further commercial development.

In the second scenario, the academic entrepreneur developing the technology may choose to spin off a company to take the technology further down the commercialization path (see the chapter “Intellectual Property: Commercializing in a University Setting”). In the early phase of the technology development, the academic entrepreneur may try to obtain grant funding to support the development. Some of the funding sources may include Small Business Innovation Research (SBIR), Small Business Technology Transfer (STTR), and R01 grants from the National Institutes of Health (NIH), the National Science Foundation (NSF), the Centers for Disease Control and Prevention (CDC), the Department of Defense (DOD), and the Defense Advanced Research Projects Agency (DARPA) (see the chapters “SBIR/STTR Grants: Application Guidance”). A clearly targeted clinical application with well-defined clinical needs, technology gap, and target population is crucial for the success of the grant applications, as well as for the eventual success of commercialization and clinical adoption. For this reason, the academic entrepreneur should engage and include team members with clinical and diagnostic expertise early in the technology development process (see the chapter “Building a Successful Startup Team”). Funding agencies also have various programs—e.g., I-Corps (see the chapter “I-Corps as a Training Tool for New Technology Development”), the Technology Niche Analyses Program, the Commercialization Accelerator Program, and the Concept to Clinic: Commercializing Innovation Program—that offer the grant awardees help in commercialization. Assistance offered through these programs may include market and customer discovery, product development mentoring, business strategy and outcomes, regulatory and reimbursement strategies, pitch coaching and networking, etc (see the chapters “Resources at Academic Entrepreneurship Centers” and “Reimbursement Strategies and CPT Codes for Device Development”). These programs are targeted to academic teams/companies at specific development phases, so it is critical to select the appropriate programs, as they typically require an intensive time investment. Simultaneously with or subsequent to grant funding, the academic entrepreneur may try to obtain venture capital funding or industry contracts to support

the technology development, clinical validation, and regulatory approval, and to grow the value of the company (see the chapters “Accelerators and Incubators”, “Angel Investors” and “Seeking Venture Capital Investment”).

Clinical Implementation of IVDs

Regulatory approval does not guarantee impactful clinical implementation and adoption. Several hurdles may prevent novel IVDs from being widely adopted. These include lack of exact match between technology and clinical needs lack of understanding in current and envisioned clinical care pathways; no demonstrated clinical utility and user-ability; suboptimal user experience, engagement, and support; and negative health economics. A lack of supporting health infrastructure may also prevent impactful implementation. In order to overcome these hurdles, the technology development team/company needs to conduct a clinical needs assessment and a care pathway analysis early on, and engage academic and clinical stakeholders throughout the process. The stakeholders are described in the next section. As an example, the development pathway for novel point-of-care technologies, from clinical needs assessment to clinical implementation, is presented in Wang and Kricka (Wang and Kricka).

Obtaining Expert Counsel

There are several important stakeholders in the development process of IVDs, besides the technology developer. These include clinicians, clinical laboratorians, health economists, patients, service providers, and payers. In order to achieve maximal adoption and impact of the IVD technology, counsel from these stakeholders should be obtained. An academic environment can provide access to a large pool of candidate stakeholders, but it is important for the academic entrepreneur to also reach outside their institute and engage with other organizations, using nondisclosure agreements as needed to protect potential intellectual property (IP). In addition, an academic institution will likely have a technology transfer office that can assist with this process (see the chapter “Working with the University Technology Transfer Office”). Subject matter experts and other stakeholders may also be engaged through ad hoc interviewing or a scientific advisory board. The contract terms and costs will vary depending upon the level of engagement.

A sample checklist with questions for different stakeholders during point-of-care technology development, optimization, and clinical adoption is summarized in Wang and Kricka (Wang and Kricka). Refer to Figure 1 and Table 4 for the pathway and checklist questions for point-of-care diagnostics development and clinical implementation (Wang and Kricka). Most aspects can be extrapolated to other types of IVDs.

Conclusion

There are multiple ways academic entrepreneurs or clinicians can lead or participate in the development, commercialization, and clinical implementation of IVDs. Contributions may be made in clinical needs assessment, technology development, clinical validation, commercialization, and implementation.

Resources

1. FDA CLIA database of approved IVD assays and devices:
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm>.
2. Centers for Disease Control and Prevention (CDC) website on CLIA, law and regulations, documents, test complexity, CLIA laboratory database search, and test reference materials: <https://wwwn.cdc.gov/CLIA/Default.aspx>.
3. FDA website on IVDs, including information on LDTs:
<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm>.
4. American Association of Clinical Chemistry (AACC) website:
<https://www.aacc.org/>. The website also has information about annual scientific programs meetings and expositions. These provide up-to-date educational, clinical, regulatory, and industry insights into clinical laboratory science and the IVD industry.
5. International Federation of Clinical Chemistry and Laboratory Medicine website:
<http://www.ifcc.org/>. This organization expands the global reach of the vision and practice of laboratory medicine and IVD. The website includes information about relevant conferences and congresses.

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