Electronic health records are “digital” and their use is widespread today. But, relative to the care patients received ten years ago, has healthcare for most patients on most days been “transformed?” Similarly, the number of drugs paired to companion diagnostics has doubled multiple times, especially in oncology. But do most people seeing a doctor today have healthcare encounters that are “transformed” by precision genetic medicine? Again, probably not.

There is another kind of digital impact that is occurring right now, and it is transforming or even creating new industrial sectors in the genomic laboratory industry. This article will highlight some of these changes. They are occurring at two levels. The first level is a transformation of what it means to be “a laboratory” which is fully energized to provide services through new horizons of digital capabilities, especially in oncology. This is the creation of “Lab 3.0.” The second level is the level of industry structure, as never-before-seen categories of companies emerge and segment the lab industry (or the lab test delivery system) in new ways. These changes will make new winners and leave behind bystanders in at least some parts of the laboratory industry.

For everyone who cares about the delivery of precision medicine — whether in biopharma, the regulatory industry, investors, or clinical healthcare providers — it’s important to understand the changes and forces at work.

**Digital Capabilities Are Supporting “Lab 3.0” – A Major Metamorphosis**

In the 1990s and early 2000s, consolidation and acquisitions led laboratories to get much bigger, but the basic functions didn’t change much. Phlebotomists drew blood, samples were moved around and acquisitioned, then automated platforms ran laboratory tests and reports were issued. Thankfully, at least more and more of the handling of reports became electronic rather than by paper or fax, but that was primarily a change at the far end of the work chain. Because most lab tests are relative commodities, competition on price is inevitable, and financial pressures led toward solutions based on economies of scale. To support these crucial economies, laboratory management worked to make their internal operations as well-digitized and efficient as possible.

Changes in the healthcare ecosystem like Accountable Care Organizations led to Lab 2.0. Lab 2.0 finds that it has to be more tightly integrated in the rest of the health system, smoothly synched with health system electronic records, and with better management of reference lab tests and other integrated approaches to utilization management such as esoteric test formularies. The 2016 handbook “Utilization Management in the Clinical Laboratory” by Kent Lewandrowski and Patrick Sluss shows how this new approach to laboratory management integrates the lab much more tightly with the overall goals of the healthcare system in which it is found.

In just the last year, in the U.S. we are seeing a new breed of lab that I call “Lab 3.0.” While it’s currently represented by a few special startups, Lab 3.0 will be something completely different, a metamorphosis of a clinical laboratory into a configuration that is only partly “laboratory” in the traditional sense. (Figure 1).
Several real world examples in the U.S. in 2016/2017 are focused on genomics at the “Lab 3.0” level, offering a new constellation of services far exceeding the capabilities of Lab 1.0 and Lab 2.0. See Table 1, but remember that these examples are representative only, and all information in this article is based on publicly available websites or trade journals.

By spinning out as independent entities, the Lab 3.0 entities can retain important ties with their parent institutions but also stand alone as entities attractive to independent investors. Three examples are OmniSeq, with origins in the Roswell Park Cancer Institute in Buffalo, New York; Sema4, with origins in the Icahn School of Medicine at Mount Sinai Medical Center New York City; and NAVICAN, with origins in the Intermountain Healthcare integrated hospital and clinic system in Utah. All aim to serve patients nationally, thus similar to traditional or publicly held reference laboratories. But each is setting up unique constellations of offerings that Lab 1.0 or Lab 2.0 can’t produce.

To highlight a few labs and their offerings. OmniSeq (which has announced a close distribution partnership with a more traditional lab, Labcorp, Inc.) has high aims to directly tackle the dilemmas that confront clinicians struggling with patient and drug selection in immuno-oncology. Much has been written about the confusing relationships among different FDA-approved drugs with distinct biomarkers (such as one-off monoclonal antibodies.) A new independent collaboration called the “PD-L1 Blueprint Project” (supported by FDA, American Association for Cancer Research, other associations, and several biopharma companies) is attempting to address harmonization issues. OmniSeq has developed a proprietary multi-technology panel approach called “Immune Report Card” to integrate reports on total mutational burden, immuno-histochemical assays, RNA sequencing, and other biomarkers on each patient. The program has its own website, http://immunereportcard.com/ and represents a stretch goal beyond the hopes of any traditional hospital-based laboratory.

<table>
<thead>
<tr>
<th>Representative Lab</th>
<th>Parent Institution</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>OmniSeq</td>
<td>Roswell Park Cancer Institute, Buffalo</td>
<td><a href="http://www.omniseq.com/">http://www.omniseq.com/</a></td>
</tr>
<tr>
<td>Sema4</td>
<td>Mt Sinai Medical center, New York City</td>
<td><a href="http://sema4genomics.com/">http://sema4genomics.com/</a></td>
</tr>
<tr>
<td>NAVICAN</td>
<td>Intermountain Healthcare, Salt Lake City</td>
<td><a href="http://Navican.com">http://Navican.com</a></td>
</tr>
</tbody>
</table>

Figure 1: Representative models show key functions of Lab 1.0, Lab 2.0, and Lab 3.0.

Figure 1: Three representative examples of innovative “Lab 3.0” entities created in the last two years.
NAVICAN's website offers a wide range of offerings that are the hallmark of Lab 3.0. It has begun by establishing formal corporate alliances with global high tech giants like Royal Phillips and Illumina. But NAVICAN aims to wrap these technologies into “a comprehensive end-to-end solution” to help patients and physicians harness “precision genomics, clinical analytics, and patients services” for cancer management. “TheraMap” is the name of its end-to-end clinical and molecular support for remotely located clinicians and patients. For example, NAVICAN can not only acquire specimens and provide genomic test reports on a patient’s tumor, but will provide molecular tumor board clinical services as well. Another service is “therapy access.” NAVICAN states, “Other companies stop at genomic profiling. NAVICAN provided experienced treatment navigators...to facilitate drug or clinical trial access.” Potentially, NAVICAN is leveraging clinic-level capabilities for off-label drug access and clinical trial access developed at the parent health system, Intermountain, but available for distant patients after their biopsy is genomically assessed at NAVICAN. As a spinout entity, NAVICAN was able to raise $15M in Series A funding in mid-2017 to fund operations and growth. Note that many of the services provided are likely to have a strong digital component: tumor boards at a distance or a new implementation of telemedicine, with remote genetic counselors and remote patient navigators who likely have access to sophisticated databases of clinical trials and best practices for drug access, electronic prior authorization, and electronic claims appeals.

In an October 2017 podcast on Proof of Concept, Eric Schatz, CEO of Sema4, describes the rich digital genomics and big data plans for their clinical genomics laboratory. Schatz was previously Chief Scientific Officer at Pacific Biosciences, a sequencing company. Schatz described his twin vision for a growing clinical genomics laboratory running in the black, while creating innovative new bioinformatics databases and leveraging them. He noted that different pools of investors could only understand one side of the vision or the other – either they liked the wetlab but were numb to the big data vision, or they liked where the big data vision could lead and thought the functioning clinical wetlab would just hold it back as a management distraction. In short, Lab 3.0 will be a new type of entity that just doesn’t fit in the traditional boxes of either a clinical laboratory or a “big data” tech company.

Entirely New Layers of Companies Are Creating New Industry Niches
The healthcare system is still figuring out how to provide large-scale clinical genomics, such as exomes. It’s not an area that the the big U.S. multi-billion dollar national labs have ventured into yet, although they have been able to successfully enter more straightforward areas of clinical genetics, such as BRCA testing and Lynch syndrome testing. Every year, more start-up companies are being developed to service some aspect of the digital (e.g. bioinformatics) needs of genomic test clinical laboratories. One schematic view of this “digital genomics industry” is shown in Figure 2. Again, as in our discussion of Lab 3.0, digital genomics companies shown are representative and the table is not all-inclusive. We’ve organized the companies in a few major groups, even though no two companies in this space are alike.

To give some examples of how these digital genomics companies present themselves, MolecularHealth originated as a wetlab for tumor genomics and differentiated into a software-only offering. MolecularHealth states that its “Dataome” technology platform “mines and structures millions of evidence-based molecular and clinical data sources. Healthcare professionals can deep dive into a knowledge base that contains curated biomarkers of drug response, resistance, and toxicity.” They provide “bioinformatics software to process raw sequencing data” and “a work space for your medical experts to generate customizable clinical reports.” Compare that description to MolecularMatch’s offering, which allows health organizations to “augment their current offerings by incorporating our automated molecular knowledge platform,” adding that “our proprietary technology delivers the deepest and broadest oncology genomic information.” And quoting from a June 2017 press release from 2bPrecise and Mayo Clinic, 2bPrecise is described as “an EHR-agnostic cloud-based precision medicine platform” which will overlay “knowledge sources to guide and enable clinical genomics at the point of care.”

Solutions that Cross and Link Institutions
While their business models and services are not the same, companies like Syapse and Flatiron do share a high-level vision in wanting to fill the large gap between the power and complexity of genomic data and what traditional institutions are able to handle with conventional electronic health records and laboratory information systems. In addition, both provide a potentially powerful means of making healthcare data in precision medicine more uniform and allowing collaboration across community clinics and larger academic institutions that share similar ways of organization clinical data in oncology. For example, retrospective clinical outcome research and clinical trial enrollment may be sped up.

Big Box Entrants
Notably, most of the largest information technology in the world, like Microsoft, IBM, SAP, and others, have initiatives in genomics and life sciences big data. These include cloud-based solutions and innovations in artificial intelligence, like IBM Watson, that have potentially rich applications in the life sciences. In some cases, the most promising startup companies in this space may be acquired into these global giants. In other cases, digital health startups may prefer to remain nimble and independent with their
specialized platforms, or grow toward an eventual initial public offering as the best path forward. Whether the biggest impact in digital genomics comes from companies like IBM or from startups like Fabric Genomics may depend on the necessity of quite large capital investments and other economies of scale.

Bioinformatics: Oncology, Non-Oncology, or Both

In Figure 2, we’ve listed a range of companies (and again, it’s not all-inclusive) that provide bioinformatics that help innovative genomics labs produce better and faster services locally where the sequencing occurs. Some of these, like GenomOncology, focus on applications in cancer precision medicine, whereas others, like Translational Software, have focused initially on pharmacogenetics for a range of drugs such as antidepressants and other medications outside of oncology. Other companies support exome and genome analysis for any clinical indication, where, for example, Edico Genomics provides sophisticated top-end server and software services that can speed genome and whole exome assembly and analysis.

Virtual Cell Biology

Yet another approach aims to bring clinical genomic data through a “great leap forward” from the status quo, in which cancer mutations in tumor cells are simply associated with drug therapies through a “look up table.” Companies in this space aim to utilization all the multi-dimensional information available from multi-hundred gene analysis to predict drug therapies and favorable outcomes by using in silico models of the individual tumor’s unique cell biology.

Other Novel Genomics Businesses

In Figure 2, rather than being upstream of a clinical lab report, companies such as Concert Genomics and Evicore are found at the far side of the precision medicine ecosystem, the one where providers interface with payers. These companies aim to provide services that allow
companies aim to provide services that allow genetic tests to be chosen more accurately, and some of them aim to make payer processes like pre-authorization of services to proceed more accurately and faster. Like other categories in this table, the companies listed each have distinct business models. Concert Genetics sees itself as a bioinformatics company that makes data from sources like federal genetic test registries more clinically actionable, whereas companies like Evicore may focus on assisting payers with evidence review processes (e.g., technology assessment). As companies in this space become more pivotal to decisions by providers and payers, lab entities from Lab 1.0 to Lab 3.0 will all need to learn to work collaboratively and efficiently with these evolving parts of the healthcare marketplace.

**Conclusion**

Most of our clinical attention is properly focused on how many drugs are paired with combination diagnostics, and whether these diagnostics are being used all the time for the right patients and conditions. At the same time, the delivery system that provides genomic testing for patients is rapidly evolving. New lab entities with much more sophisticated ranges of integrated services aim to reduce the friction and delays and mistakes that may plague patient care, for example, between genomic reporting and access to tumor boards or genetic counselors. Various forms of informatics and telemedicine promise to be quite helpful and can be directly embedded in Lab 3.0 or seamlessly provided through partnerships that are invisible to the clinician and patient.

Labs increasingly recognize their role as repositories for enormous amounts of genomic information, which when handled with appropriate privacy safeguards will turbocharge a learning healthcare system in precision medicine. This is a key part of the mission of labs like Sema4. Meanwhile, digital genomic offerings in the form of “software as a service” may harken the end of the era when “it takes a village” of costly and rare PhD-level staff to provide top-line sophisticated genomic services only at the largest academic medical centers. Numerous companies are competing to allow both large and smaller medical centers to provide state-of-the-art bioinformatics interpretation for their patients by interweaving local wetlab next generation sequencing with remote and constantly improving bioinformatics capabilities.

Although the emergence and proliferation of companies and business models may entail some “creative destruction” over the next five years, the creativity and energy going into digital genomics solutions will surely speed to progress of precision medicine. We should be prepared for a new version of the genomics lab industry that will be a “metamorphosis” toward new models rather than just an incremental evolution.