Editorial

Genes in the Basement, Postmortem Genetic Testing…and 3 (New) Realities

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We all have a treasure trove of things—squirreled away in knick-knack drawers or long-forgotten boxes in the basement, storage lockers, and parents' homes. Things we tell ourselves will someday have value if we just wait long enough. Every pathology department has things too—the glass slides and paraffin blocks of specimens long since diagnosed and discarded, all tucked away in the far recesses of hospitals and storage warehouses, waiting for a time to reach their full potential. A select few of these even manage to be resurrected each year, some for a retrospective analysis of one marker or another, others to settle a diagnostic or medicolegal matter. Most, however, sit idly in file cabinets and storage facilities, out of sight and largely forgotten, reminiscent of the final scene in Raiders of the Lost Ark.

See Article by Baudhuin et al

Those materials, however, still have great value. Among pathologists, this is not exactly a secret—archived slides and blocks have long been appropriated for developing new stains, defining diagnoses, and understanding disease pathogenesis. And when modern genetic testing methods arrived, many had visions of Jurassic Park-style moments, unlocking the secrets embedded not in amber but in paraffin.

Unfortunately, most of the promise of such materials has languished.

Genetic testing methods to date have largely focused on peripheral blood and carefully preserved tissues gathered from living patients. Applying the same techniques to the stuff in the basement has not been easy. The manipulations involved in tissue fixation, processing, and storage all cause damage to the genetic material, and extracting the goods from wax blocks is not straightforward either.

There is an even larger set of obstacles raised when the tissues of interest come from a postmortem evaluation: by definition, autopsy materials represent largely dead and dying tissues, rarely collected in ideal circumstances, and decaying at suboptimal temperatures for extended periods of time. Even if adequately collected, samples are often pickled for extended duration while sorting through the logistics of ordering and paying for genetic tests on a decedent who is not covered by insurance any longer. In the era of Sanger sequencing, these obstacles were just too much to overcome. However, like the original Star Wars, next-generation sequencing has provided a new hope.

The molecular autopsy has been in the pathology lexicon for a while, but the techniques have not yet matured. Nevertheless, the potential for identifying genetic variants that can spell early mortality in next-of-kin remains a tantalizing prospect. Approaches in this pursuit have included postmortem blood storage and snap-frozen tissue. Neither is perfect, and both require storage resources that are not universally available. Fortunately, routine tissue sections continue to be fixed in formalin, embedded in paraffin, and stored under the presumption that they would someday be used.

Now it is time to go get those blocks out. In this issue, Baudhuin et al[1] describe a methodology for postmortem materials that performs reliably well for gene panel next-generation sequencing. They have successfully analyzed sudden death autopsy cases using formalin-fixed paraffin-embedded samples and dried blood spot cards—stored at room temperature for varying lengths of time (from 6 months to 15 years)—to identify mutations associated with sudden cardiac death. They combine high quality extraction and purification techniques, targeted gene capture to enrich for those genes most relevant to study, and next-generation sequencing, a technology intrinsically less sensitive to DNA fragmentation. Indeed, part of the beauty of next-generation sequencing is that one must first intentionally fragment the DNA to the same size pieces that occur as an unintended consequence of genetic decay and standard formalin-fixed paraffin-embedded processing. Their methods are elegant and straightforward and should be readily reproducible by other groups.

Now, we can do back to the unsolved cases and get some answers. And with this new set of tools, 3 realities (re)-emerge.

Reality No. 1: There Is Tremendous Value in Pathology Department Archives

All those blocks in the basement have value beyond justifying the existence of storage companies. So-called discarded tissue is a cornerstone of medical investigation; with the new Common Rule,[2] the US Government has recently buttressed support for this with ethically appropriate, more accommodating rules concerning the use of such material. For the foreseeable future, we will be able to glean insights into human disease using bona fide samples from representative patient material.

Beyond guaranteeing a mechanism for quality control, all those warehoused blocks can contribute to ongoing medical

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circ Cardiovasc Genet*. 2017;10:e002008. DOI: 10.1161/CIRCGENETICS.117.002008.)

***Circ Cardiovasc Genet* is available at http://circgenetics.ahajournals.org**

DOI: 10.1161/CIRCGENETICS.117.002008

care. Material gets stored specifically for the possibility that new methods and approaches will become available later. Now that we can theoretically perform genetic testing on formalin-fixed paraffin-embedded samples, we can apply diverse genetic testing approaches to rethink diseases, diagnoses, and treatments—not only for deceased patients but also for their living relatives.

Reality No. 2: The Autopsy Still Matters, a Lot

Blocks cannot be saved unless we actually perform the autopsies. For surgical specimens, all is well, but for the postmortem examination, ongoing declining autopsy rates threaten our ability to archive such material. The current methodology from Baudhuin et al[1] is an extremely promising start; it is safe to say that new and better analytical methods will also certainly evolve—all the more reason to ensure that material is saved.

But autopsy is so much more than that. Autopsy provides education into anatomy in ways few other procedures can. It provides additional information in cases even when the cause of death is clearly known. It is the ultimate quality control and assurance procedure, allowing for detailed evaluation of every medical intervention and providing a chance to reconcile all those with the chart. Autopsy ensures that diseases that can threaten the populace are appropriately identified and provides insights into how to prevent those illnesses. And extracting genetic information from autopsy material significantly expands what the postmortem examination can shed light on.

Reality No. 3: Sudden Cardiac Death Need Not Strike a Family Twice

Infectious disease is the obvious target of such investigations, but genetic disease affects the populace as well. Surviving relatives are at risk of the same disease. By identifying the specific genetics at play in a decedent, we are armed with the knowledge of what to look for in everyone else.

Our society and our science are not ready to screen the entire population for hereditable diseases—we would find things we do not want to know and additional things that we do not know what to do about. Instead, we have to accept for now that some people are going to succumb to cardiomyopathy, channelopathy, and other causes of sudden cardiac death. However, with the work by Baudhuin et al,[1] we do not need to let a second person in a cohort die. We can elucidate potential causative genetic defects and then screen family members to evaluate risk. By not screening everyone—and just those who might actually carry the disease—we can better allocate resources while ensuring that no family experiences a second tragic loss from the same mutation.

This mission is just as valid for medical examiners and coroners. While perhaps a stretch of their mandate and funding models, it is ultimately their role to protect the public. In the same way that they provide evidence against a murderer who might kill again, documenting genetic disease has the potential to identify genes that can also take another life. Simply raising the spectre of a genetic component might trigger screening in some families, but nothing drives care as solidly as a firm diagnosis. It is time for the system to embrace this just as much as any other cause of death. Baudhuin et al[1] have removed an important barrier to the process.

Disclosures

None.

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KEY WORDS: Editorials ■ death, sudden, cardiac ■ genetic techniques ■ genetic testing ■ tissue fixation

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Circ Cardiovasc Genet. 2017;10:
doi: 10.1161/CIRCGENETICS.117.002008
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1942-325X. Online ISSN: 1942-3268