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Perspective

Neonatal Screening and DNA Forensics: An Underappreciated Connection

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Abstract

Neonatal screening involves collecting dried blood spots on filter paper from essentially all newborns in most countries. These specimens are a potential store of each child's DNA. In some locales, laboratories have stored these spots for 50 years. There are risks and benefits associated with having these specimens in storage. This opinion article argues that now is the time to weigh the balance for keeping such spots in long term storage and choose to do so in a fashion that preserves the rights and privacy of the DNA's source or decide not to keep the specimens indefinitely and choose when to discard them.

Keywords: Newborn; Phenylketonuria; Sickle Cell Disease; DNA Fingerprints; Short Tandem Repeats; DNA Privacy

Abbreviations

CODIS: Combined DNA Index System;

HIPAA: The Health Insurance Portability And Accountability Act;

PCR: Polymerase Chain Reaction;

PKU: Phenylketonuria;

RFLP: Restriction Fragment Length Polymorphism;

STR: Short Tandem Repeat

Introduction

Dried blood spots on filter paper collected from newborns as specimens for screening constitute an intersection between that screening and DNA forensics. This paper calls attention to that overlap and its implications because few individual states / regions responsible for screening in the USA and few countries with similar programs have yet paid serious consideration to those implications.

Neonatal Screening

Development of a bacterial inhibition assay to detect phenylketonuria (PKU) by Robert Guthrie was the first impetus for neonatal screening [1]. The rationale for creating this test was the prior development of a limited phenylalanine diet [2]. The diet was effective in preventing mental retardation if started when the patient was very young, but it could not prevent loss of intellectual ability if initiated too late after birth. Thus prevention of PKU's devastating effects required screening for PKU in newborns. This model led to tests for other disorders where early intervention could save intellects, lives or both [3-5].

Although the ability to test for PKU received most of the initial attention from the medical community, the test's inventor felt that the use of dried blood spots on filter paper as specimens was actually his greater contribution because

they

1. Simplified blood collection to a simple heel prick.

2. Enabled easy mailing of specimens individually or en masse to a central testing laboratory.

3. Permitted easy labeling of collection information on the same piece of paper.

4. Allowed long term storage in a fashion similar to retaining a card file (Guthrie, R., 1970, personal communication to MDG).

These factors encouraged development of a screen for sickle cell disease [6] despite the challenges involved in detecting homozygosity for Hb S after elution from a dried blood spot in the presence of the newborn's excess of fetal hemoglobin. Subsequent experience with mandatory neonatal screening for sickle cell disease in New York State showed that screening saved lives and led to better management.

After collecting dried blood spots for newborn screening began to spread, it also became apparent that early intervention could often ameliorate a disorder like hypothyroidism leading to screening for it [7] which increased enthusiasm for neonatal screening and made its acceptance even more wide spread. The recent occurrence of the 50th anniversary for the original paper [1] has stimulated excellent recent reviews for scientific [8] and lay audiences [9].

The advent of polymerase chain reaction (PCR) amplification of DNA [10, 11], inspired recognition that filter paper spots of blood from newborns were ideal specimens for recovering DNA for PCR amplification [12]. Indeed, the dried blood spots are by definition dehydrated, the drying leading to a lacquer like coat that helps to prevent access of water that would lead to loss of the DNA in the sample. Micro-extraction of DNA from filter paper spots of blood from newborns soon proved feasible [13] with the first successful PCR DNA diagnostic success being used for sickle cell disease [14] as in one of the initial reports for PCR [11].

DNA Forensics

When the first paper on DNA profiling [15] appeared, this author already had a passing acquaintance with its, Professor Sir Alec Jeffreys, due to a shared interest in globin genes. Thus the utility of a hypervariable minisatellite repeat sequence did gain attention for many applications, with the demonstration on forensic issues quick to follow [16, 17].

DNA fingerprints, as they were dubbed, clearly provided a means of tracking identification, but the challenge for minisatellite repeat sequence patterns was to quantitate the chance that two unrelated individuals shared the same pattern. Instead, the frequency of Restriction Fragment Length Polymorphisms (RFLPs) could readily be evaluated after detection by single locus probes so RFLPs provided an intermediate term solution. A committee reporting to the US National Academy of Sciences recommended the use of these RFLPs [18] in part because of the potential for establishing the odds of a random match. Because of controversy particularly about the ceiling principle that was introduced to allow for inadequate population data, that report was soon replaced by another [19] although such RFLPs remained in use. The application of PCR improved the sensitivity of forensic DNA analysis which soon turned to a different type of repeat called a short tandem repeat (STR). Now many forensic laboratories rely on commercial sources for equipment and reagents to analyze STRs with the early uses contemporaneous with the latter report [20]. By selecting STRs on distinct chromosomes (in separate linkage groups), DNA forensic labs can come up with enormous odds on the likelihood that a survey of random individuals would have the specific pattern found in the forensic sample and someone who matches STRs provides alleles with a small number of countable repeats so that the data are easily reported numerically or recorded in databases such as the US national database — CODIS or Combined DNA Index System. Many states (New York, for example, has NYDIS) and regions in the US, as well as most countries maintain similar databases. Depending on the jurisdiction, one has to be convicted of a felony or at least arrested for a crime before one's DNA type is stored in a DIS in the US. In Europe the desire to cooperate among countries led to a uniform system ultimately based on STRs [21] that facilitates exchange of information [22].

How newborn screening and DNA forensics intersect via storage of specimens and PCR

In recounting some history of newborn screening, this paper has pointed out how labs are capable of recovering DNA for PCR amplification from dried blood spots. Usually the Guthrie card containing the spot also contains information about the newborn's identity and they are often stored indefinitely. For example, storage began in 1963 for those collected in Western New York where the Guthrie PKU test originated. Thus, it is readily apparent that an enterprising criminal investigator could try to gain access to a suspect's DNA for comparison to a forensic sample by obtaining the Guthrie card in storage since the suspect was less than one week old.

If the hypothetical situation just outlined occurred in the US, an enterprising attorney might argue that it would violate the suspect's Fourth Amendment protection against an invasive search. In a vigorously debated decision, the US Supreme Court recently ruled that police may take samples of DNA from persons arrested for a serious crime [23] but the rationale – to assure proper identification of the arrestee – does not apply to the scenario above. The Health Insurance Portability and Accountability Act (HIPAA), enacted in 2003, could also bear on access to Guthrie cards; but it is not clear how HIPAA applies to stored dried blood spots [24]. The key issue here is who controls a specimen's use after collection. In this context, publication of a recent best-seller on the ethical issues arising

from the development of the HeLa cell line [25] has focused popular attention on the use or misuse of a person's cells after removing them. Although the HeLa line itself originated before newborn screening and cells are much more than just DNA, the book's popularity serves to get readers thinking about the issue and can serve as a springboard for encouraging legislators to consider Guthrie cards.

Reasons why there are benefits from storing newborns' dried blood spots indefinitely include (1) having material with which to develop new tests to expand neonatal screening, (2) providing opportunities to check if an initial screen provided an incorrect result, (3) helping to straighten out the occasional, but rare, situation in which parents take the wrong baby home and (4) providing a DNA sample from a neonate for identification of remains after disaster renders it difficult to track the victim as happened for some Australians after the 2009 Victorian bushfires [26]. These rationales constitute strong reasons to store Guthrie cards indefinitely without deidentifying the neonate. So it is incumbent on the jurisdictions or regions involved with neonatal screening to perform risk / benefit analysis to decide how long to store Guthrie cards and how to assure the privacy rights of the screened persons over a long period. Newborn screening is mandatory in 49 states and the District of Columbia; it is voluntary but achieves very high coverage in the state of Maryland. States have therefore begun to consider the legal status of stored Guthrie cards with heterogeneous results [27]. Parents can request destruction after varying specific lengths of storage in Michigan, Minnesota, South Carolina, Texas, and Washington, for example [24]. In a more extreme example, Texas incinerated over 5 million Guthrie cards in 2010 to settle a law suit [28]. In contrast, some of the Scandinavian victims of the December 2004 Tsunami in Thailand were identified via access to DNA from Guthrie cards [29].

Considerations and Implications for the Future

I personally believe that long term storage is proper but that each screening lab should have a clear policy set by the appropriate governing entity about access to the samples. Depending on the jurisdiction, how the access policy gets implemented is likely to vary. Given the broad implementation of newborn screening around the world and the wide variety of governing systems, it is likely that multiple approaches will develop, ideally in a culturally sensitive fashion that respects the rights and interests of the newborn who was the source and of the newborn's parents who wish to raise a child to healthy adulthood.

An example of how the locale affects the legal basis for a search in the past returns us to the work of Sir Alec Jeffreys who applied his ability to make DNA fingerprints to forensic samples [17] in the now famous case of Colin Pitchfork, recounted at length in book form [30]. During the investigation, the local police tried to collect blood for DNA typing from all males in the village where two murders had occurred; their investigational technique was acceptable in the UK but impermissible in the US. (Ironically, Mr. Pitchfork bribed another male to impersonate him; so he almost escaped until his impersonator revealed the subterfuge. It is also of interest that another accused was found innocent via this early application of DNA typing and the events are now so historical that Mr. Pitchfork could be released within a year.)

If Guthrie cards are to be stored for future uses, one must also consider how to store them, for what purposes, under what restrictions and for how long. A serious and comprehensive analysis of the issue was offered in 1996 [31], but the first author's state subsequently destroyed its Guthrie cards [28] to settle a suit so it is worthwhile to re-examine the advice. Samples should be stored at 4°C (or even frozen if recovery of protein activity in addition to DNA is desired), sealed in a low permeability bag under humidity control. Sample retrieval needs to be documented when it occurs. The paper also provides some circumstances other than the Australian and Thai disasters where compassionate forensic access seems reasonable but otherwise recommends that a subpoena be necessary for forensic use. Although some programs do not store samples for more than 6 months, the disasters provide an argument for storage for well over 21 years. Although the survey represents the views of a sample from only 6 states in the US, a recent study of attitudes should help to inform decisions and the need for more public education [32]. Clearly different cultures and jurisdictions may end up with varied approaches, but serious consideration needs to be given or events will sweep past a country's or region's circumstances without a decision being in place.

While it is the intent of the author to stimulate action on the potential use / misuse of Guthrie cards for forensic purposes, it is also worth noting that Next Generation DNA Sequencing has made it possible to sequence genomes from dried blood spots soon perhaps in a fashion that is economically acceptable. Indeed, the National Institutes of Health of the US announced plans to evaluate sequencing newborns via such samples as well as to evaluate some of the ethical concerns [33-35].

The ability to recover DNA sequences could bring some access to dried blood spots under the aegis of the US Genetic Nondiscrimination Act [36]. Perhaps it also indicates a need to amend that bill. It certainly underlines the necessity that jurisdictions where newborn screening takes place should define the status of access to the Guthrie cards containing dried blood and identifying information before events affect newborns' privacy rights.

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on the breadth of interaction between DNA forensics and neonatal screening remain attributable to me, however. I dedicate this perspective to the late Professor Robert Guthrie and Professor Sir Alec Jeffreys whose seminal developments inspired it.

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