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CORRESPONDENCE

Response to "Newborn dried blood spot samples in Denmark: the hidden figures of secondary use and research participation"

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In "European Journal of Human Genetics" 2019;27:203–210 by Nordfalk and Ekstrøm (N&E) describe and criticize the usage of the Danish Newborn Screening Biobank (DNSB) for "secondary research purposes" [1]. Their literature search by January 2018 led to 104 articles using one or more samples from DNSB for purposes allegedly beyond the primary screening, and they estimate a usage of up to 794,157 samples corresponding to 37.5% of all samples in the biobank.

These numbers are fundamentally incorrect and we disagree on N&E criticism of sample usage for screening improvements and research. The authors were in contact with DNSB prior to their study, but they did not contact DNSB again before publication as to avoid major factual errors, distorted categorizations and misinterpretations.

Newborn screening was implemented nationally in Denmark in 1975, and Statens Serum Institut began to store surplus of dried blood spot (DBS) samples at −24 °C from the newborn screening in 1981. An information brochure given to the parents before the blood sampling describe the purpose of the screening, and plainly describe the purposes of storage and how to prevent storage and/or use of samples for research [English version in supplementary material]. As described in the article by N&E, by Danish law all blood samples can legally be stored without explicit informed consent. Their later use for additional analysis are however conditional on approvals of each separate project from the Research Ethics Committee and the Danish Data Protection Agency. According to the law, the use of samples for research projects require informed consent, but the Research Ethics Committee can waive this requirement if the project is carried out with anonymous samples and does not in any way imply health-related risks or may burden the participants. The same applies for access to existing laboratory data and the large amount of clinical data available from the Danish Health Data Authority. Ethical approvals are however not required in general for projects dealing with quality assurance and improvements of routine medical services, including newborn screening programs.

N&E suggest that although the screening program is legally voluntary, it may not always be perceived as such by the parents, and that consent for storage and subsequent use of the samples is embedded in allowing the samples to be taken. We disagree. The same law applies to newborn DBS samples as to any other blood sample taken by the Danish health care system. In addition, the information brochure given to the parents before the blood sampling clearly states that the screening depends on parents' consent and describe how to prevent storage [supplementary material].

Of the 104 articles listed by N&E in their supplementary material as articles using newborn DBS samples for secondary research purposes, at least 41 are of high relevance for newborn screening. Of these, at least 13 deal with the newborn screening in Denmark and disorders screened for in the routine program or in the former informed consented voluntary program (article from the N&E list No: 26, 48, 51, 56, 67, 77, 78, 79, 81, 82, 83, 86, and 88). The voluntary program ran from February 2002 till February 2009, where in average 85% of all parents consented to let their newborn participate in an expanded screening program for additional 19 disorders. We find the classification of these articles as *secondary research purposes* inappropriate as validating the performance is an integral part of running a screening program and involves reporting of screening and ancillary results. In addition, at least 12 articles evaluate the possibility to screen for new disorders not included in the program at the time (article from N&E list No: 38, 45, 59, 85, 87, 90, 94, 95, 99, 100, 102, and 104). Some of these articles are mainly or solely based on existing data from the screening program or analysis of fresh routine samples after

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informed consent and have thus very little or nothing to do with the biobank, see below. Finally, at least 16 of the articles are technical method articles dealing with new possibilities and challenges of analyzing DBS samples (article from N&E list No: 4, 5, 8, 15, 20, 39, 42, 60, 32, 64, 70, 71, 72, 73, 84, and 98). Diligent method development and expansion of the screening by adding new serious disorders to the program is an obligation for a newborn screening center, especially if unique resources are available as in the DNSB. Hence, it is misleading to categorize the work performed in these 41 articles as *secondary research purposes* in relation to newborn screening. These activities are ancillary and are required for current and coming high-quality screening, which adheres to national and international standards.

The discovery and characterization of any new disease biomarker in DBS samples taken a few days after birth may open up for new expanded or improved screening of newborns. The predictive value of a neonatal biomarker for a disease is essential for its applicability in newborn screening. Biomarkers with high predictive values may often be identified in studies of simple monogenetic disorders and may thus be of direct importance for newborn screening programs. In most studies of complex disorders with uncertain etiology, it is however less likely that a single biomarker with high predictive value may be found. Thus, the remaining 63 of the 104 articles in the list of N&E may in some contexts be characterized as *secondary research purposes*, but numerous biomarkers with low predictive value are often found in such studies, and combined they may be useful in future newborn screening employing more complex algorithms than those that are used today. Moreover, our knowledge of the mechanisms behind the disorder will increase by such studies to the benefit of prevention and treatment. N&E state that the type of research using DBS samples from the DNSB has changed to research "not in any way related to the primary purpose". In particular, they criticize usage of samples in studies of mental illness. We disagree. The purpose of newborn screening is to identify serious congenital disorders as soon as possible in order to prevent severe disabilities and death. Mental illness are among the greatest challenges humanity face and falls well within this category of disorders.

Of the 794,157 samples N&E estimated used from DNSB, at least 747,084 are not stored samples from the biobank. They are fresh routine samples from consented pilot newborn screening studies, or the data presented are already existing data from the newborn screening program. Three articles from the N&E list account for the 747,084 misclassified samples and explain three incorrect sudden big increases in sample usage year 1999, 2002, and 2012, presented in their paper Fig. 2. Article No 94 by Lebech et al. Lancet 1999, is an informed consented pilot newborn screening study for congenital toxoplasma infection employing an extra 3.2 mm punch taken from 89,873 fresh routine DBS samples as they arrive to the screening laboratory. No 88 by Sørensen et al. Clinical Chemistry 2002, is a technical study presenting a new improved method for detection of toxoplasma gondii-specific IgM and IgA antibodies run in parallel with the established routine toxoplasmosis screening method. The study use an extra punch from 137,861 fresh neonatal DBS samples taken for the routine neonatal screening program, Screening for toxoplasmosis was included in the Danish newborn screening program from 1999 but was stopped 2007 due to lack of clear clinical evidence of treatment. No 51 by Andresen et al. Molecular Genetics and Metabolism 2012, is a study over MCAD-deficiency in Denmark based on already acquired data from 519,350 newborns participating in the previously mentioned informed consented voluntary screening program that included MCAD or the subsequent routine screening for MCAD starting February 2009.

In the early years of the DNSB the retrieval of samples for research purposes were limited and detailed records of projects incomplete. However, based on biobank records from year 2000 and forward, where the majority of samples from the Danish Newborn Screening Biobank have been retrieved, it is our estimate that from 1981 till 2017 approximately 220,000 samples have been retrieved. Of these, approximately 40,000 samples have been used mainly by Statens Serum Institut for quality assurance and expansion of the Danish newborn screening program, and approximately 180,000 samples have been retrieved for use in scientific projects.

N&E find it problematic that the three "most productive authors" of their listed 104 articles are current or former employees at Statens Serum Institut. A simple count from the 104 articles reveal however that 500 scientists from 140 institutions, including all major Danish universities and hospitals, are authors. The three employees are first authors on 8 articles of which 7 are new method developments making it possible to analyze important compounds in DBS samples. Danish Center for Neonatal Screening at Statens Serum Institut has focused on developing and mastering such techniques, and has made these available to a large number of researchers. This work is basis for many recent publications using samples from DNSB. How scientists can access samples in DNSB is well described on the website for the Danish National Biobank (www.nationalbiobank.dk).

DNSB is not legally responsible for projects approved by the Research Ethics Committee and the Danish Data Protection Agency and do not have complete records on which biological compounds the sample have been analyzed for nor to what extend the resulting data have been published. In addition, it is difficult to determine the total number of published articles employing samples from DNSB, but according

to our records the last three years it is at least 20 in 2016; 19 in 2017, and 20 in 2018. N&E suggest that uncertainty about details in the reporting of the use of biobank samples could lead to distrust in the population. We agree, and will provide more information on the DNSB website as to avoid misperceptions. It is our experience though, that the proportion of citizens requesting their samples (or their children's samples) removed from the biobank is very low (<0.1%) even at times when Bio-banking activity is subject to public debate. Thus, the public support appears to be solid, which most likely is a consequence of the clear system of governance involving scientific ethics committees and the absence of any reports of abuse through more than 36 years of function.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Reference

1. Nordfalk F, Ekstrøm CT. Newborn dried blood spot samples in Denmark: the hidden figures of secondary use and research participation. Eur J Hum Genet. 2019;27:203–10.