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CORRESPONDENCE

Setting a new standard in cystic fibrosis newborn screening illustrates controversial issues as new data emerge

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To the Editor:

The article by Sasaki et al. [1] sets new standards for performance in newborn screening (NBS) for cystic fibrosis (CF) and also highlights a variety of laboratory, genetic and communication/counselling issues while raising fundamental questions about screening strategies. The metrics reported from the Republic of Ireland (ROI) programme are the best ever achieved with regard to sensitivity and positive predictive value (PPV) at 99.4 and 84.1%, respectively. Although the PPV benefitted from the high incidence of CF in the Irish population, it is much higher than usually observed [2]. Another important CF NBS metric, the age of diagnosis, was not reported. Nor have we been provided with information on surveillance methods to ensure identifying missed cases. Assuming efficient, effective follow up to ensure diagnostic confirmation and treatment initiation within 2–4 weeks, the ROI has achieved a model CF NBS programme.

The ROI's impressive outcomes are attributable to well-planned, superb CF NBS methods. It was my privilege during 2009 to advise their public health leaders and participate initially in the planning. A critical and comprehensive assessment was performed over 2 years in association with specialists in genetics, particularly David Barton, and in CF as a Paediatric Respiratory Consultant with NBS experience in Australia, Barry Linnane, stepped forward to join the National Steering Group for the Introduction of CF NBS in Ireland. The investment in a thorough planning process has paid dividends for this region with its high incidence of CF and the world's highest frequency of the p.Gly551Asp variant. The National Steering Group quickly decided to employ the two-tier IRT/DNA method with a single bloodspot sample and was rewarded for their judgement. One of the issues addressed early on was the strategy or philosophy of the programme—leading to a decision to focus on "classic CF cases," i.e., those with one or more symptoms and a sweat chloride value of ≥60 mmol/L. This traditional definition, however, does not mesh well with NBS because symptoms are unlikely unless meconium ileus is present and a growing body of evidence reveals that ≥30 mmol/L is consistent with a CF diagnosis in infants [3]. In addition, the concept of "borderline" or intermediate sweat chloride values has been reassessed recently [3]. Frankly, the dogma surrounding a ≥60 mmol/L discriminant for diagnosis is obsolete. Moreover, in this era of routine early diagnosis and CFTR modulator therapy in an effort to preserve organ function, "classic" is no longer meaningful in my judgment.

In practice, the NBS strategy and its outcomes are typically determined by the screening algorithm, particularly with regard to the cutoff value of IRT and the number and composition of variants included in the *CFTR* panel. These aspects are discussed in detail as part of the new CF NBS Guideline [4] published recently by the Clinical and Laboratory Standards Institute (CLSI)—the product of an international team working during the interval of the ROI study. As described therein, the role of genetic analyses often becomes the determinant of diagnoses, but the increasing diversity of the reproducing populations in Europe and North America argues for expanding *CFTR* panels.

The ROI's decision to use a floating IRT cutoff value set at the 99th percentile, around 60 ng/ml, was wise and provided advantages over fixed cutoffs and in comparison to more complicated, multistage algorithms [5] that may require a "safety net" that IRT/DNA protocols can avoid [4]. Their *CFTR* panel was large enough for 2011–2017 but may need future expansion, although the use of "extended DNA sequencing" helps meet the need for addressing the increasing genetic diversity of their reproducing population. During the planning process, the ROI National Steering

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Group also gave special attention to the variant p. Arg117His (also known as R117H)—common in populations derived from Europe and amenable to treatment with ivacaftor but controversial with regard to its clinical significance. The ROI took the bold step of excluding this variant from their panel, and Sasaki et al. [1] should be commended for discussing the p.Arg117His results candidly. Most other regions have included this common variant in their *CFTR* panel, and some such as the USA could not exclude it, nor poly-T tract, determination, on medical and perhaps ethical grounds. But more long-term research is needed on patients with p.Arg117His and either 5T or 7T.

The ROI made a decision that is common in European countries but not North America to "minimise detection of unaffected carriers and CFSPID." Although CFSPID was not described until 2015 [6] and is now better understood [7], the issues were well known to the National Steering Group. Both CFSPID and *CFTR* heterozygote detection are byproducts of IRT-based NBS that create follow-up issues and necessitate expert genetic counselling to mitigate parental misunderstandings. Yet, with emergence of recent data [7, 8], the practice of selecting screening strategies to avoid CFSPID cases and the group often called "heathy carriers" can be challenged. It has been learned in recent years that at least 10% and perhaps as many as 44% of children initially classified as CFSPID will develop symptoms of CF and/or a higher, diagnostic sweat chloride level [4, 7, 8]. Thus, it is predictable that the ROI's limitations inherent in short-term studies will be overcome by longer follow up of the 32 CFSPID cases and will eventually identify at least 3 more CF patients who may even appear "classic."

With regard to CF carriers, despite the assumption based on Mendelian autosomal recessive inheritance, the notion that CF carriers are healthy was never supported by sound evidence nor subject to scientific scrutiny until recently. On the other hand, CFTR-related disorders such as pancreatitis and bronchiectasis have been reported in carriers for over 20 years [9], and a recently reported, large study by Miller et al. [10] has revealed that those with one *CFTR* variant have a significantly increased risk for 57 of 59 CF-related diagnostic conditions. Their observations and others reviewed elsewhere [11] challenge the concept of "healthy carriers," which could become another refuted CF dogma. More fundamentally, as we have learned with sickle cell trait [11], the concept of recessive may be misleading. In fact, the new data suggest that the significance of having a single *CFTR* variant is more complex than we ever imagined. If an uncertain prognosis for carriers is proven, it will be prudent to reconsider genetic counselling messages to ensure honest disclosure. But, clearly, more research is needed on CF carriers, and excellent NBS programmes like that of the ROI will provide that opportunity.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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