Newborn Screening for all Identifiable Disorders with Tandem Mass Spectrometry is Cost Effective: The Negative Case

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Abstract

Tandem mass spectrometry has become increasingly popular as the preferred technology for detecting inborn errors of metabolism in newborn screening programmes. Its sensitivity and specificity for detecting numerous inborn errors has been well documented. However, there are continuing questions about whether the technology should be used to the fullest when such usage may mean detecting and reporting analytical findings that could lead to diagnosing conditions for which clinical outcome is unclear and treatment may not be needed, or treatment efficacy may not yet be proven and cost effectiveness is unlikely. As part of a friendly debate to educate conference attendees on both sides of somewhat controversial issues, these 2 papers at the conference presented some of the information supporting or questioning the cost effectiveness of full scan usage and reporting in tandem mass spectrometry newborn screening. Reported here are some of the questioning arguments.

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The introduction of tandem mass spectrometry (MSMS) was indeed a great leap forward for newborn screening, and after over a decade of experience of this technique, evidence about its performance is accumulating. The most important information needed about a newborn screening programme is the clinical effectiveness of early diagnosis, an estimation of the possible harms that may be involved to families (mainly due to false positive, and perhaps false negative results, and stigmatisation) and some estimation of the financial costs.

Cost effectiveness compares costs and outcomes of 2 different actions – in this case, screening or not screening. For screening, it is of major interest, because costs and outcomes are multiplied across large populations. Cost more than outcome often affects government decisions.[1] But there are problems in its assessment. The cost of the intervention, screening, can be measured reasonably accurately; the effect of the intervention on the health of the population can also be measured, at least in the short term. But the increase in health outcome is sometimes the avoidance of death. It is not always clear how to combine these 2 sets of data.

There have been over a dozen studies of the cost aspects of tandem mass spectrometry. The majority of these have relied on many unproven assumptions rather than actual screening data, and over half have focussed primarily on medium-chain acyl CoA dehydrogenase (MCAD) deficiency.[2-12] Almost all these concluded positively, usually that screening uses "more resources…but attains better health outcomes"[3] or similar findings. Two studies[13,14] used actual newborn screening data and compared this with data from unscreened comparable populations, both coming to positive conclusions. In our Australian study,[13] we measured the within-laboratory cost of screening, including depreciation of instrumentation, costs of follow-up for true- and false-positive cases, and all costs of treatment and healthcare in the first 4 years of life. The actual costs per screened patient were more than those per patient for the non-screened, but the life-years gained and deaths averted altered the balance in favour of screening. The missing cases (those never diagnosed) among the non-screened complicate the analysis. The current weight of evidence, however, is in favour of screening being cost effective. So am I changing sides in this debate? Not really.

Let us examine again the motion: "That newborn screening with tandem mass spectrometry *for all identifiable disorders* is cost effective". The studies referred to above cannot

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address that question for many reasons:

- There is a lack of data on the outcome of clinically-diagnosed cases for many of the disorders;
- Far more cases are found by newborn screening than by clinical detection;
- Some of these cases are "extra" cases of a disorder that usually but not always produces symptoms, but some are cases of disorders which now appear benign, or nearly so.

And then there are other reasons why screening might not be cost effective:

- There is a risk of litigation in relation to missed cases, or healthy children who have received unnecessary treatment;
- There is an extra burden expected for laboratories and clinicians to deal with the cases of all sorts, including the false-positives.

Let us examine some of these points:

In many countries and states, there is a lack of systematic data on the unscreened population. The costs of not screening might be smaller than estimated, as there will have been unknown numbers of deaths, and additionally many affected patients with less serious conditions might never receive any healthcare.

It is certain that more cases are found by screening. We do have good data on the unscreened population in Australia: for MCAD deficiency, there are more than twice as many cases found by screening.[15] Our later data suggest that the ratio for other fatty acid oxidation disorders is more than 4 times as many, and for some organic acid disorders – eg 3-methylcrotonyl CoA carboxylase deficiency, also a similar increment. Going hand-in-hand with this, we may be finding the wrong sorts of cases. Several disorders detectable by current MSMS strategies were rarely found before screening occurred, and appear benign. Short-chain acyl-CoA dehydrogenase deficiency is a case in point and there are several others. Many of the extra cases may receive life-long treatment where none was needed[16] which will increase costs. The treatment could have adverse effects – also an increase in costs which may be hard to quantify. For MCAD deficiency, we know this is a potentially fatal condition. But screening identifies fewer patients with the common (northern European) mutation, c.985G, and several (8 in our first 50 cases) with a mutation known to be "mild", c199C, which has never been found in patients with symptomatic MCAD deficiency.[17] It would be a bold physician who would assert that such cases were at no risk ever, so they too will almost certainly be "extra" patients.

Will there be a risk of much extra litigation? If a disorder in the long term is accepted as benign, could physicians be sued for unnecessary treatment? Certainly if a very restrictive diet is prescribed unnecessarily this could be the case.[16] What if a case is missed? Homocystinuria is an example where we know that no pyridoxine-responsive case has ever been found by newborn screening, but non-responsive cases may also be missed. Those detected benefit greatly, but this will not be a comfort to the parents of patients missed by the screening and subsequently handicapped. All of screening is a balance between sensitivity and specificity – danger of missing cases versus the adverse effects, including cost, of false positive results.

The motion specifies, "all identifiable disorders". So do we want to include, for example, the isolated hypermethioninaemias, most examples of which appear entirely benign? We can easily detect histidinaemia in the same laboratory run as routine MSMS screening. This disorder we certainly know we do not want to detect, as it has clearly been shown to be a benign quirk. Do we currently know what disorders need treatment and might benefit from early diagnosis? I have recently addressed this question in relation to dietetic management.[16] The studies cited earlier have been largely theoretical, with many doubtful assumptions. Our own study did not show that screening was less costly than not screening, (although it suggested a balance in favour of screening, when including averted deaths) and no study has yet looked at "screening for all identifiable disorders".

I believe that MSMS screening can be cost effective under some circumstances, but not if there is screening for all identifiable disorders. We certainly need to consider screening for all disorders for which there is credible evidence of a substantial risk of an adverse outcome unless there is early detection and effective treatment. But we should not institute screening for disorders where there is insufficient evidence of adverse clinical outcomes, and no rational intervention proposed or needed. That can only lead to unnecessary distress and increased costs. Because of this, I suggest that the motion, "that newborn screening with tandem mass spectrometry for all identifiable disorders is cost effective" cannot be sustained.

Disclaimer: This was a debate. The views presented here do not necessarily represent the views of the authors or those of the US Health Resources and Services Administration, or the New South Wales Newborn Screening Programme administration.

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