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Prenatal testing, cancer risk and the overdiagnosis dilemma

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In March, US company Sequenom revealed that its MateniT21 non-invasive prenatal test (NIPT) has detected potential cancer in some pregnant women (see BioNews 793). As well as receiving information about their fetus, around 40 of the 400,000 or so women who have had this test have been informed that they may have cancer. One example of this was Dr Eunice Lee, who had investigations following an abnormal NIPT result that identified a 7cm colorectal tumour, which was then surgically removed.

This is a good thing, right? Women in the prime of their lives receiving information that may catch a cancer early. But, we suggest, it is not this simple. So-called liquid biopsies lead to ethical issues that go beyond the matter of using a test for one thing and finding out about something else. They are also a prime example of the problem of overdiagnosis. Before diving into this particular biopsy pool, we need to think carefully about what might be under the surface.

Overdiagnosis is hard to define, but, loosely, an overdiagnosis is a correct diagnosis that doesn't benefit a patient. It occurs when a test finds something that, if left alone, would regress, or never become symptomatic. Although in practical terms the line between false positives and overdiagnosis can be blurry, the conceptual distinction is this: an overdiagnosis is a correct diagnosis that doesn't benefit, while a false positive is an incorrect test result: a finding that is not actually true. Both can lead to harm, such as having unnecessary medical interventions. They also consume valuable and often scarce health resources.

We know neither the extent of overdiagnosis nor the false-positive rate for suspected cancer detection following NIPT. The latter will be measurable soon enough, but pinning down rates of overdiagnosis will be difficult.

Study designs make for costly research, and it is hard to study what happens without treatment as we all naturally want intervention when something is found. We do know that in this instance, 14 of the 40 women (35 percent) did not, as it turns out, have cancer. And it is unlikely that all 26 women shown to have cancer had a form of cancer that needed to be investigated or treated at that particular point in time. They will now think of themselves as 'cancer survivors' or 'near miss' cases but, without NIPT, some of them would likely have lived their whole lives not knowing they'd had cancer.

In genetics, we are attuned to pay attention to incidental findings - results a test turns up that weren't initially expected. When a test result suggests something that can be identified and

intervened in, there is a strong professional inclination to report that risk. Information is an empowering tool of the trade. Often we claim that there is an ethical imperative to pass it on to patients. But here, while we know there is a risk, but we cannot quantify the endpoint. Some - like Dr Lee - will clearly benefit, but not all will.

This type of information also calls into question the deeply held belief that information, if it exists, should be shared with the person it pertains to. Should we be reporting results if we don't know whether those results have any potential to benefit the patient?

Scholars working on ethics and overdiagnosis urge us to look beyond the individual. Our natural reaction to stories like this is to frame the context in terms of 'individuals saved'. Indeed, this is what personalised medicine is all about. But this can also come at a cost to collective health that should not be ignored.

This is a profoundly utilitarian problem. If we take a health utility perspective, we can't deny that Dr Lee appears to have benefited from this information. But this must also be weighed against the possibility that other pregnant women will go through unnecessary testing, or risk their pregnancies by having treatment they don't need. What trade-offs of harm should we be willing to accept in order to promote wellbeing in one individual among that population?

Because this question is difficult to answer, what is needed is a procedurally just process to talk about it directly. Part of this may require us to let go of our strong anchor to individual health. We may also need to reconsider whether reassurance should be seen as a benefit if the patient's cancer worry is entirely an artefact of testing. These are not easy questions, but ones we must answer. The NIPT detection example is just one of many that will soon be upon us.

The prenatal context of this test is also relevant. Pregnancy tends to be a time of significant contact with health professionals. Whether or not prenatal testing is chosen, pregnant women themselves experience myriad checks and monitoring. It is an exciting time but can also lead to anxiety. How should we reason around potential divulgence of information that may or may not be significant when there are also other ties, such as the impact of worry or treatment on a fetus?

Detecting cancer through NIPT may, in some cases, save lives. But at this early stage, and given the largely unregulated context in which NIPT is being carried out, we suggest that there is not yet an irrefutable ethical imperative to pass this information on.

We must also consider the wider population-based implications of receipt of this information. This may require us to question long-held assumptions that all cancer is life-threatening, and that all information is worth sharing. It may also mean trade-offs between individual wellbeing and collective health. At this early and unproven stage of liquid biopsies, especially in a prenatal context (where cancer diagnosis is not the object of testing), we need to work together to deliberate the trade-offs and obtain more data. None of this will be easy.