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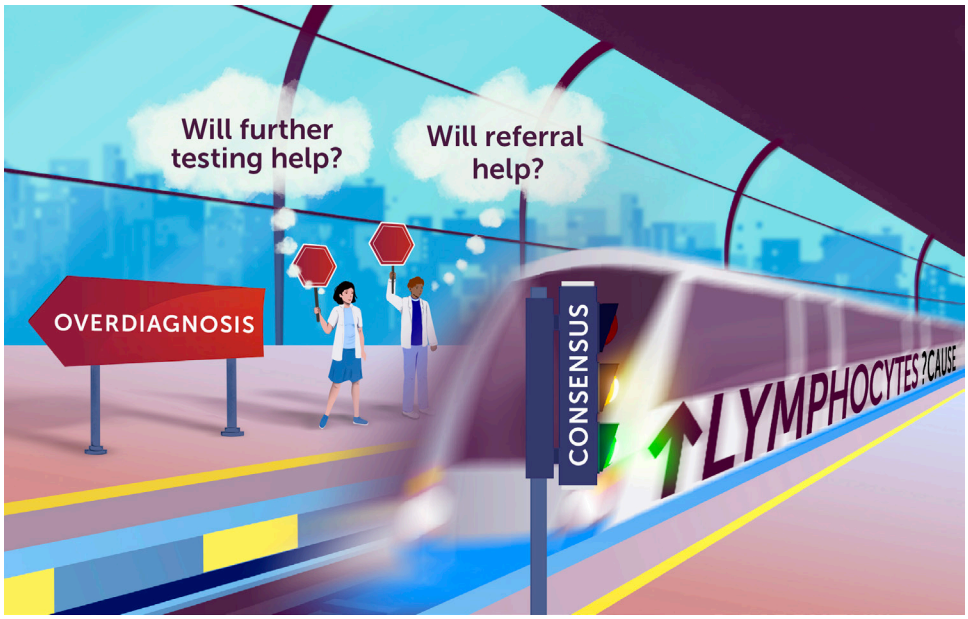
Why Do We Diagnose Monoclonal B-cell Lymphocytosis? Five Questions

Stephen Hibbs[1], Esca van Blarikom[1]

Correspondence: Stephen Hibbs, *HemaSphere* Scientific Editor (s.p.hibbs@qmul.ac.uk).



Before Mrs Baker had even entered the room, I had a sinking feeling in my stomach. I had first seen her six weeks ago: a 71-year-old woman who had routine blood tests as part of medication monitoring, and was found to have a raised lymphocyte count of around 7×10^9/L on three occasions. She had no B-symptoms, no palpable lymphadenopathy or organomegaly, and the rest of her blood count was normal. My colleagues suggested that their pragmatic management would be to request immunophenotyping and to discharge her from clinic if the result was polyclonal. I took their advice, but the test revealed the root of my sinking feeling: the results showed monoclonal B-cell lymphocytosis (MBL). As I puzzled over how to explain the (in)significance of MBL to her, I also found myself wondering: why do we diagnose MBL in the first place?

If there is an underlying disorder, shouldn't I diagnose it? This assumption holds for many invisible and asymptomatic medical conditions. There is a clear rationale for diagnosing asymptomatic hypertension, diabetes, or colonic adenomas, as action can be taken now to prevent damage later. But diagnosing MBL or other asymptomatic lymphoproliferative disorders (eg, chronic lymphocytic leukaemia (CLL) or follicular lymphoma) in Mrs Baker does not provide her with any new treatment options. MBL is associated with a small increase in the risk of infections and solid tumours, and reduced response to vaccinations, but none of these risks can be mitigated by making the diagnosis. A diagnostic label can be defined as "overdiagnosis" when it does not produce a net benefit for the diagnosed person.[1] So, a more pertinent question might be, what will making the diagnosis *do* for Mrs Baker?

What will change for Mrs Baker by knowing she has MBL? The general practitioner (GP) referral to the haematology clinic may have already instilled the fear that there must be significant

[1]Wolfson Institute of Population Health, Queen Mary University of London, United Kingdom

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concern for her health. Now, with the MBL diagnosis Mrs Baker becomes a haematology "patient-in-waiting"[2]—somewhere in between being well and unwell. As a patient-in-waiting, Mrs Baker will undergo indefinite monitoring and surveillance to identify when she becomes potentially treatable. Although she only has a 1%–2% chance each year to develop symptoms requiring treatment, she may start personally identifying as a patient. This can produce real effects: rates of self-described anxiety and depression in CLL patients are higher in those on expectant management than in those receiving active treatment.[3] There is no published research into the harms of an MBL diagnosis, but the patient-in-waiting experience may produce similar harms.

If I had not tested Mrs Baker, would my practice be questioned if she later develops symptomatic CLL? Fear is often a powerful motivator for our practice—specifically the fear of missing something. This fear is likely to be behind the GP's initial referral—a test detects a risk for which a care provider feels responsible regardless of whether they can exert any control over the prognosis. The GP dutifully carries over the risk to the haematologist whose sense of responsibility for the risk creates an urge to fully investigate, even if it results in overdiagnosis. But Mrs Baker would only need treatment once she develops symptoms, meaning that her bodily sensations are the best monitor. This will probably never happen for her. Does diagnosing her years before the possibility of symptomatic illness benefit Mrs Baker in any way?

If this testing practice makes so little sense, how did we get here? We practice in the context of a wider society that is becoming increasingly focused on risk. As a society, we are increasingly uncomfortable with uncertainty, although life itself has not become riskier. In medicine, this trend can be seen in our shift from understanding disease based on a patient's experience of symptoms towards understanding diseases as indicators for future adverse events. In practice, doctors spend expanding amounts of their time identifying factors that help predict the future, rather than addressing suffering in the present.[4]

Can we do anything to resist this trend? It is helpful to consider the example of investigating hereditary thrombophilia. The UK guidelines recommend against testing for hereditary thrombophilia in most settings, on the grounds that diagnosis causes anxiety and confusion, without guiding management. In this case, the thrombosis community came together to take responsibility for clarifying the risk. Yes, people with hereditary thrombophilia might get a thrombosis. But if nothing is done differently by knowing this predisposition, the diagnostic benefits do not outweigh the harms and cost of testing. Could lymphoproliferative disorder experts recommend the same? Yes, a person with asymptomatic lymphocytosis might one day develop a symptomatic lymphoproliferative disorder—but would it have helped to know in advance? There might be specific situations where diagnosis is helpful, analogous to thrombophilia testing in some contexts around pregnancy. But for many asymptomatic people, the harms of immunophenotyping outweigh the benefits, and reaching this consensus amongst experts could empower individual clinicians to resist overdiagnosis.

The examples of MBL and hereditary thrombophilia raise an important question that we should continue to pose what constitutes disease, what warrants medical investigation, and how does the same test help some patients and harm others? With these fundamental questions in mind, I imagined how Mrs Baker's journey could have been had I responded differently to the initial concern from her GP.

When the GP referral for Mrs Baker came through, I sat down with a colleague to discuss what to do. Unsatisfied with my approaches to previous patients, I asked them the question: why do we bring patients like Mrs Baker to clinic? They argued that she might have CLL or some other lymphoproliferative disorder, and it is our job to find out. I'd felt the same before. But now I pushed back—"If this lymphocytosis indicates something that needs our intervention, then it will declare itself in her symptoms if and when they arise." With this as a guiding thought, and a renewed appreciation of the harms of overdiagnosis, I began my response to her GP…

AUTHOR CONTRIBUTIONS

SH and EvB discussed the concepts and wrote the article together.

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