The Journey to Ancient Ithaca: addressing the diagnostic odyssey of rare disease through systems-level interventions

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Abstract

The "Diagnostic Odyssey" is a common pathway of misdiagnosis and diagnostic delay that many patients with rare diseases find themselves forced to negotiate, just as Homer's character Odysseus struggled for an entire decade after the Trojan War to return home to Ithaca. Rare diseases are to some extent, by virtue of their rarity, always going to resist diagnosis. Nonetheless, there are several interventions that we can implement in the healthcare system to limit the delays and frustrations that patients with rare diseases experience between the onset of their symptoms and the initiation of treatment for a correctly diagnosed condition. These include adaptation of medical education to better reflect the integration required in the environment of modern healthcare, the uptake of new technologies and in-practice resources directed at diagnosing rare disease, and the utilization of patient navigators to accompany patients and advocate for them on their journeys to diagnosis. The "Diagnostic Odyssey" therefore represents an actionable target for all healthcare providers – and students – to work towards eliminating.

JS is a 48-year-old woman with a past medical history significant only for childhood asthma, presenting to her family physician after two weeks of shortness of breath on exertion and symptoms of allergic rhinitis. She is prescribed an inhaler and an anti-histamine, which provide her with limited relief. Over the next year, she develops a cough and worsening shortness of breath, prompting her to return to her family physician who makes a finding of nasal polyposis. JS's family physician refers her to a respirologist and an otolaryngologist. JS's respirologist sees her several months later and performs pulmonary function tests, making a diagnosis of worsening asthma and prescribing additional nebulized medications. Her referral to the otolaryngologist is not received by their office, and the consultation is forgotten. One year later, JS begins to experience paresthesia and weakness in several digits of each hand. She returns to her family physician and, three months later, sees a neurologist who makes a diagnosis of mononeuritis multiplex and refers her to a rheumatologist with a suspicion of vasculitis. Three years after the initial onset of her symptoms, JS's rheumatologist performs a full biochemical, pathological, and radiological work-up for systemic vasculitis, diagnosing her with eosinophilic granulomatosis with polyangiitis (EGPA). JS begins taking systemic glucocorticoids and her symptoms finally resolve. Between the onset of her symptoms and the treatment of her condition, JS was laid off by her employer and suffered repercussions to her mental health.

The case of JS is not unusual, except that her diagnosis of EGPA was made relatively rapidly: a 2016 study by Cottin et al. quotes the mean length of time from the onset of asthmatic symptoms to diagnosis as 11.8 years with a standard deviation of 18.2 years.[1] EGPA is not unique in this regard. The path to diagnosis for rare diseases is commonly long, and it is weathered by ailing patients who spend years seeking a cause for their symptoms.[2] For example, the average delay from symptom onset to diagnosis of cblC cobalamin metabolism defects is reported to range from 3 to 240+ months,[3] and this same delay for early-onset dementia averages 4.4 years.[4] Rare diseases are typically defined by a population frequency of 1/2000 persons or less,[5] but these conditions affect more than 3 million Canadians.[6] The diagnostic odyssey – a common pathway of misdiagnosis and diagnostic delay that many patients with rare diseases find themselves forced to negotiate – is a widespread, frustrating, and harmful misadventure.[7]

The etiology of the diagnostic odyssey is multi-factorial and, unfortunately, many of these factors resist elimination. Intuitively, physicians are better prepared to recognize common diseases; both because their training likely focuses on those afflictions which they can expect to see more frequently, and because once in practice their clinical experience statistically affords them less exposure to rare diseases.[8] Consequently, physicians are inherently not as well-equipped to diagnose and treat uncommon diseases.

Despite this barrier, the diagnostic odyssey is in many ways actionable from a systems perspective. Even if some amount of delay in the diagnosis of rare disease cannot be altogether extinguished, there are several levels at which carefully designed interventions can contribute to reducing the time patients with rare diseases spend struggling to find validation and treatment for their symptoms. Some of the interventions for which effectiveness has already been demonstrated include: the incorporation of probabilistic diagnostic decision support systems – such as IBM's artificially-

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intelligent supercomputer, Watson[9] – in clinic settings, which suggest the possibility of rare diseases on the basis of consistency with case presentations;[10,11] the use of specialized search engines such as FindZebra, which have been demonstrated as more effective tools for diagnosing rare diseases than non-specific search engines such as Google or PubMed;[11] the creation of centers specifically focused on the diagnosis and treatment of rare diseases, like in China, have been credited with enabling a faster escape from the diagnostic odyssey;[12] and new technologies such as next-generation DNA sequencing have demonstrated efficacy for making diagnoses of rare diseases with high sensitivity and high specificity, presenting – especially as costs decrease – a possible future for panel testing in uncertain cases.[13] In parallel with these advances, there appears to be a role for education: an international survey performed in 2013 indicated that a majority of physicians felt that additional training around rare diseases would support faster diagnosis.[14]

The perpetual diagnostic odyssey warrants continued development and adoption of new ideas to reduce the time-to-diagnosis for patients with rare diseases. The demonstrated utility of these previously-tried interventions does, however, illuminate several of the core causes of delayed diagnosis: a lack of integrative provider education, limited resources that proffer easy access to information on uncommon conditions, and a medical system structure in which patients can "fall through the cracks". This present article aims to highlight and provide perspective on the future of this task, through the suggestion of several novel interventions which have not been previously proposed or studied. For physicians, these interventions include updates in medical education with a greater focus on integration, as well as the utilization of new in-practice diagnostic tools (not unlike those which have previously been successful) designed to help address rare diseases. Beyond physicians, there is also a unique role in rare disease medicine for patient navigators, in aiding patients during their journey to diagnosis.

Medical education can perpetuate the diagnostic odyssey by presenting medicine in silos. In traditional block curricula such as that described by Li et al (2018) with reference to Chinese undergraduate medical education (representative of many countries' training programs), students learn topics related to one body system or one specialty before moving on to the next.[15] In the United States, this same format has been demonstrated to effectively teach the information within each block, but discourage integration across these blocks.16 Our training appears to divide us into experts of disparate fields, with a more limited understanding of the interfaces between them.[16,17] Consequently, it is my experience that students graduate into a practice in which they struggle to form cohesive teams with specialists of other areas. This is compounded by the bureaucracy that underpins the healthcare system and preserves the division between the silos in which we find ourselves. In a hospital setting, I have observed specialists in one field argue with those in another about who ought to be responsible for a patient's care. We fax referrals and seldom follow up to make sure they were received – a large proportion of referred patients do not even appear to ultimately see the provider they were referred to.[18,19] At times, it is possible that the tension between resource stewardship (which includes limiting unnecessary referrals) and quality patient care can contribute to diagnostic delays.[20] It is inevitable that no one provider can know everything, and therefore be in a position where they can easily diagnose rare diseases with multi-system presentations, but it is reasonable to expect that through improved connectedness, we will be able to limit those spaces between specialists where patients on the diagnostic odyssey are temporarily or permanently lost to follow-up. At the level of medical education, this means a greater focus on healthcare systems integration. This may involve a departure from block-based curricula to an alternative such as a "spiral curriculum – a method characterized by repetitive exposure to topics on a longitudinal basis, which has been evidenced in some settings but not yet studied in the context of rare disease education[21,22] – as well as increased training around what circumstances would warrant casting a wide diagnostic net to appropriately bring in specialists from many fields in order to make the diagnosis of a rare disease.

For those already in practice, several novel tools now exist to aid physicians in recognizing and diagnosing rare disease. Orphanet, for example, is a resource dedicated to mapping out rare diseases in ways which are accessible to health providers, patients and families, and researchers.[23,24] By leveraging technological innovations like intelligent search algorithms and mass information storage, these types of databases can put a wealth of information about rare disease at the fingertips of all stakeholders who participate in the diagnostic odyssey.[24] These resources vet experts to contribute information on rare diseases, and make it available to everyone through search engines specific to uncommon diseases.[23] For physicians in practice, utilizing resources like Orphanet when the possibility of a rare disease arises can shorten the time from symptom onset to diagnosis for patients with unexplained presentations (and who have already, unfruitfully, seen several specialists).

Finally, a third intervention which can alleviate the diagnostic odyssey is the implementation of patient navigators, particularly those with specialized training in the context of rare diseases. These professionals can help patients to negotiate the labyrinthian medical system, in which it is easy to get lost between providers, guiding them through their diagnostic journey and advocating for those patients who are temporarily forgotten within the system.[25] Patient navigators comprise a relatively new profession within the medical system, but one already evidenced to bolster the continuity of patient care and help to connect patients with the right resources – whether that is the appropriate doctors or reliable sources of information.[26] It is known that patients with undiagnosed rare diseases tend to have many physicians involved in their care, which can make for a confusing medical record and increasing diagnostic uncertainty.[27] In these circumstances, there is a unique role for patient navigators to forge therapeutic relationships with patients so that they do not have to navigate the diagnostic odyssey alone.

The diagnostic odyssey associated with rare disease is a consuming journey that begins surreptitiously, for many patients, beginning with the onset of a first symptom. It is a major contributor to dissatisfaction with the healthcare system, and also to morbidity and mortality in the context of diseases for which treatment delays can be of great consequence.[28,29] Despite the intuitive nature of delayed diagnoses for diseases which are unfamiliar to physicians, we can – by embracing integrative medical education, creating and utilizing high-quality resources geared towards rare disease diagnosis, and accepting help from other professionals such as patient navigators – develop our environment into one which more effectively serves the patients who are negotiating the twists and turns of elusive diagnoses. In the Odyssey of each patient, these inter-

ventions represent opportunities for us to help an individual reach their diagnostic Ithaca.

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