in the projected financial and human toll of a global strategy versus the continuation of the status quo, Menzies and colleagues demonstrate the true costs to the United States of failing to invest in a global tuberculosis control strategy.

This thoughtful and detailed analysis by Menzies and colleagues shows that investing in a comprehensive approach to tuberculosis control in high-burden settings—both directly and through global partners—makes sense for our nation. As the United States congress rethinks the nation's global strategy for combating tuberculosis (the End Tuberculosis Now Act), there is an opportunity to redefine our approach to global tuberculosis eradication. Menzies and colleagues have given us a strong push in the right direction. Their conclusions are difficult to refute and should be immediately adopted by advocates, policy makers, and funding agencies. ■

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PHorecasting Heritable Pulmonary Arterial Hypertension: Are We Nearly There Yet?

For individuals with a family history of pulmonary arterial hypertension (PAH), especially for those who know they have inherited the familial mutation, it must feel like they are waiting for the other shoe to drop, and yet it is by no means inevitable that they will develop the disease. Mutations in the *BMPR2* (bone morphogenetic protein receptor 2) gene are the most common cause of heritable PAH, and here we know that the penetrance—the proportion of mutation carriers who actually develop the disease—averages 27% (1). Even for females, for whom the penetrance is about three times higher than in males, more than half of mutation carriers will remain asymptomatic throughout their lifetime. So, what triggers the development of PAH in some individuals, and can we predict when and to whom this will occur?

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In this issue of the *Journal*, Amin and colleagues (pp. 1587–1589) present two case reports that give us a snapshot of clinical "conversion" from healthy to a diagnosis of PAH in two teenagers who had inherited *BMPR2* mutations (2). In the first case, a young woman had a normal right heart catheterization (RHC) at age 17, with mean pulmonary artery pressure (mPAP) of 15 mm Hg. Echocardiography performed 6 months later was also normal. Another 9 months later, shortly after starting college, she presented with a history of syncope and increasing dyspnea. Echocardiography now showed mild right ventricular dilation, and RHC revealed her mPAP had increased to 52 mm Hg. What precipitated such a rapid change? The authors speculate that environmental and/or psychosocial changes associated with moving away to college may have contributed. Hormonal birth control had also been initiated prior to her genetic test.

The second case, a 16-year-old male, had a less detailed clinical history available. Previous echocardiogram, performed at age 12 to investigate a heart murmur, was normal. PAH was diagnosed at age 16 during routine evaluation because of a family history of the disease associated with a *BMPR2* mutation. Contributing factors in this case may have included obesity, a sedentary lifestyle, and prediabetes.

Though it is impossible to know for sure what triggered the development of PAH in these cases, they emphasize the importance of PAH screening in at-risk individuals. Case 1 also highlights that the onset of symptoms can occur within months of a normal clinical evaluation, which presents a challenge in deciding the optimal frequency of screening. The current screening recommendation for mutation carriers is annual echocardiogram with follow-up RHC if there is evidence of PAH (3). Other potential screening modalities are discussed in a recent review by Kiely and colleagues (4). Amin and colleagues suggest that increased vigilance is warranted at times of significant life changes, such as puberty or starting college, which seems prudent. They also emphasize the importance of counseling adolescents as they take on responsibility for their own health and lifestyle decisions.

Are there ways that we can improve prediction of which mutation carriers will develop PAH? In the report by Amin and colleagues, case 1 is notable for a detailed clinical workup, which unusually included invasive RHC while the patient was asymptomatic. However, there was nothing in these clinical evaluations that would portend the rapid onset of PAH little more than a year later. Unfortunately, there are no molecular studies that would give insight into any infections or inflammatory changes that might have been associated. Case 2 had comorbidities that would suggest a potential proinflammatory state, but, again, the available molecular biomarkers are limited.

More detailed insight will hopefully come from the French DELPHI-2 study, in which a cohort of 55 asymptomatic *BMPR2* mutation carriers are being prospectively studied. Some initial findings, published in a recent abstract, report that two females already had mild PAH by RHC at inclusion (mPAP of 25 and 26 mm Hg), with otherwise normal clinical parameters (5). Twelve subjects had exercise pulmonary hypertension of unclear significance, two of whom were later diagnosed with PAH at follow-up. Importantly, serial blood samples are being collected, which may reveal novel biomarkers of early PAH. Several recent studies have already identified transcriptomic, proteomic, and metabolomic signatures that are diagnostic of PAH and can predict outcomes (6–9). It will be very interesting to learn if any of these markers are also altered in presymptomatic individuals, or if they change around the time of PAH diagnosis. Similarly, a recent study of induced pluripotent stem cell–derived endothelial cells identified pathways that differed between PAH-affected subjects and unaffected family members who carried the familial mutation (10). It would be intriguing to know if those pathways can distinguish between the carriers who later develop PAH and those who do not, albeit a more complex experiment than simple blood-borne markers.

So, are we nearly there yet? Can we forecast who will develop PAH and when? No, but the current report from Amin and colleagues highlights how rapidly PAH can manifest, and DELPHI-2 promises deeper insight into both clinical and molecular screening tools. Yet the numbers will still be very small, emphasizing the need to pool data across international collaborations, such as the PAH-ICON (International Consortium for Genetic Studies in PAH). A better understanding of PAH onset in unaffected mutation carriers could identify the pathways that drive the earliest stages of the disease, potentially benefitting other at-risk groups. And then our challenge will be how to harness this information to prevent the disease, or at least arrest it in the presymptomatic stage. ■

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