In terms of clinical diagnostics, the value of ApoE genotyping as a predictor of AD risk has yet to be fully delineated. Such efforts are complicated by the notion that AD does not conform to the 1 gene–1 disease hypothesis. While the majority of Americans possess the ApoE3 allele, which is not associated with accelerated AD onset, additional risk factors such as age, sex, and familial history can play an important role (3). A phase III clinical trial (TOMMORROW) of a predictive risk-assessment algorithm examining age and APOE and TOMM40 genotype, expected to run over the next 6 years, could provide the insight to fill this knowledge gap.

An additional issue with ApoE genotyping is that AD falls into the same category as polycystic kidney disease and Huntington disease—diseases for which there are currently no effective preventative treatments or therapeutic interventions. As such, ApoE genotyping differs from other gene-associated risk assessment strategies. In BRCA (early-onset breast cancer) mutation analysis, for example, identification of a deleterious mutation can mitigate breast and ovarian cancer development through interventions such as prophylactic medications or elective surgery (4). Still, it is estimated that even delaying AD onset by 2 years could result in 2 million fewer cases of AD over the next 50 years (5). In 2009, researchers noted delayed symptom progression in type 2 diabetic patients with mild AD taking the drug pioglitazone (6). The TOMMORROW clinical trial will also explore the utility of pioglitazone in individuals deemed high risk by the age and genotype algorithm.

AD-related brain pathology precedes the onset of symptoms; a diagnosis during life is currently made through a combination of psychological and cognitive clinical criteria. As the incidence of AD is expected to grow in the coming years, identifying those at greatest risk through genotype analysis, in combination with other risk factors, will be essential for delaying symptom onset and slowing disease progression while additional therapies continue to be evaluated.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

References


Diagnostics in the Front Line against Infectious Disease

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In spite of the terrible conflicts that currently plague our world, perhaps ironically, we have never been more interconnected. An old foe that we all share is the threat posed by dangerous pathogens, the spread of which is made infinitely easier by our ability to travel large distances in short time periods within our so-called global
village. In 2014, the world health community appears to be losing the battle against infectious disease, largely from a failure to allocate adequate financial resources for diagnostics. Development of effective diagnostics for identification and surveillance of deadly pathogens is essential in preventing the spread across borders. This report, based on an article by Mark Kessel in *Nature Biotechnology*, briefly discusses the worrying lack of preparation for dangerous outbreaks and the economic burden on the diagnostics sector when things go wrong (1).

**Outbreak 2014**

In March this year, arguably the deadliest occurrence of the Ebola virus since its discovery in 1976 was reported in West Africa. According to the WHO, this latest outbreak emanated from a single individual infected in a remote area of southeastern Guinea. Failure to contain the spread of the virus has since resulted in confirmed cases being reported in several countries well outside the region. This case illustrates how easily the plight of one affected individual can wreak havoc on global health security and exposes our inadequacies in tackling the problem at the source. Countermeasures based on effective diagnostics are often hit hardest in an outbreak situation and are clearly inadequate to meet the challenge, particularly in remote parts of the world.

**Diagnostic Dilemma**

In February 2014, the Global Health Security Agenda (GHSA) was created to detect and respond to infectious disease threats. The GHSA aimed to achieve this by improving disease monitoring and developing tests for the most dangerous pathogens, of which diagnostics was to be a major component. There was to be an emphasis on delivering accurate and timely testing capability at the point of care, while minimizing the risk to healthcare professionals. In reality, however, the project was hopelessly underfunded. The $40 million allocated by the GHSA in 2014 is not nearly enough to accomplish the goals of the diagnostic component alone. As laboratorians, we are well aware of the challenges in developing and introducing new tests capable of performing to the required standards. Unbeknown to the politicians, this process is infinitely more difficult when operating in challenging working environments, such as sub-Saharan Africa.

**Bottom Line: Who Pays?**

The need to develop effective diagnostics requires a collaborative effort, with funding from both public and philanthropic sources. The healthcare industry is predictably reluctant to get involved. Although markedly cheaper than therapeutics, development of a complex diagnostic can still cost up to $50 million. Unfortunately, there is little financial incentive for private stakeholders to invest, particularly for these markets. Regardless of who pays, if governments are truly serious about global health security against highly infective diseases, then substantial investment is required over and above that outlined by the GHSA. Otherwise, the threat posed from deadly outbreaks will remain.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures or Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

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