ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2018) 1-9

Alzheimer's & Dementia

Featured Article

Biomedical informatics applications for precision management of neurodegenerative diseases

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Abstract Modern medicine is in the midst of a revolution driven by "big data," rapidly advancing computing power, and broader integration of technology into healthcare. Highly detailed and individualized profiles of both health and disease states are now possible, including biomarkers, genomic profiles, cognitive and behavioral phenotypes, high-frequency assessments, and medical imaging. Although these data are incredibly complex, they can potentially be used to understand multi-determinant causal relationships, elucidate modifiable factors, and ultimately customize treatments based on individual parameters. Especially for neurodegenerative diseases, where an effective therapeutic agent has yet to be discovered, there remains a critical need for an interdisciplinary perspective on data and information management due to the number of unanswered questions. Biomedical informatics is a multidisciplinary field that falls at the intersection of information technology, computer and data science, engineering, and healthcare that will be instrumental for uncovering novel insights into neurodegenerative disease research, including both causal relationships and therapeutic targets and maximizing the utility of both clinical and research data. The present study aims to provide a brief overview of biomedical informatics and how clinical data applications such as clinical decision support tools can be developed to derive new knowledge from the wealth of available data to advance clinical care and scientific research of neurodegenerative diseases in the era of precision medicine.

Keywords: Informatics; Neurodegenerative disease; Biomarker; Clinical decision support; Precision medicine; Evidence-based practice; Alzheimer's disease; Learning healthcare; Machine learning

1. Biomedical informatics applications for precision management of neurodegenerative disease

The practice of medicine is in the midst of a modern-day revolution, driven by "big data," rapidly advancing computing power, and broader integration of technology into health-care service provision. It is anticipated that from 2014 to 2024, health-care information technology job growth is expected to substantially outpace job growth among other industries [1], due in part to the deluge of health data generated by new technologies. These data can create highly detailed and individualized profiles of both health and disease states, which can potentially be used to understand multi-determinant causal relationships, elucidate modifiable factors, and ultimately customize treatments based on individual parameters. In the case of neurodegenerative diseases (NDDs), where many questions are still unanswered and effective therapies have remained elusive, there is a critical need for an interdisciplinary perspective on data and information management to derive novel insights, generate new knowledge, improve care, and facilitate treatment discovery. Biomedical informatics (BMIs) is a

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https://doi.org/10.1016/j.trci.2018.03.007

multidisciplinary field that falls at the intersection of information technology, computer and data science, engineering, and healthcare; this interdisciplinary intersection will play an integral role in the future of medicine. The present study aims to provide a brief overview of BMIs and how novel clinical data applications can be developed to derive new knowledge from existing data to advance clinical care and scientific research of NDD in the era of precision medicine (PM). The generation and organization of big data and its application in healthcare settings depend on a scientific infrastructure that anticipates both the needs of these types of data, as well as, how they may be used. The National Institutes of Health and the National Institute of General Medical Sciences support awards such as the Center for Biomedical Research Excellence grants to support big data infrastructure and advance data science. The Center for Neurodegeneration and Translational Neuroscience is a Center for Biomedical Research Excellence–supported neuroscience enterprise with a Data Management and Statistics Core that serves as a platform for investigating how to apply big data to PM.

1.1. What is PM?

PM has recently been defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." [2]. A primary aim of PM is to link individuals with the best possible treatment for an individual's disease in the hope of improving clinical outcomes, and ultimately, patient health. Effective implementation of PM into clinical practice requires integration of translational research from a diverse array of data sources to ensure that the PM approach is firmly rooted in empirical evidence. Although individualized approaches to clinical care have been present for decades, (e.g., matching blood transfusions or solid organ transplants based on blood type), the wealth of data available in modern medicine, with all its technological advances, moves the potential for truly precise interventions far beyond what has historically been possible. NDDs present significant opportunity for development of PM interventions [3], not only because of the wealth of genetic information now available [4,5] but also because of the concurrent growth in biomarker discovery [6] and the ability to characterize the cognitive and behavioral phenotype in rich detail. Moreover, the historical approaches (e.g., one-size-fits-all treatment) have almost universally failed to uncover an effective therapeutic agent [7], which may in part be due to the incredible diversity in disease manifestations that can result from the same underlying pathology.

1.2. Biomarkers of neurodegeneration for PM

Definitive diagnosis of NDD requires positive identification of the pathologic changes occurring in the brain, which for most NDD begin decades before the onset of observable symptoms. As a result, there is considerable interest in the discovery and validation of reliable biomarkers that could be used to improve diagnostic accuracy, especially early in the disease process before the full clinical syndrome is manifest [8]. At present, body fluid analysis and brain imaging are the two principal sources for biomarker data.

1.3. Fluid biomarkers

Cerebrospinal fluid (CSF) has been a prominent target for discovery of potential biomarkers, given the possibility that it provides molecular insights into pathologic processes within the brain. For example, amyloid β-42 and tau were two of the earliest validated biomarkers in Alzheimer's disease (AD) [9], which has been refined to separate tau into total tau and phosphorylated tau [10,11]. These CSF markers have demonstrated good sensitivity to AD pathology and are widely used in both clinical practice and research. However, limited specificity [12,13] has mitigated their utility as stand-alone diagnostics, especially at preclinical stages [14]. Coupled with the invasive nature of CSF studies, recent efforts have focused on identification of potential biomarkers in peripheral fluids (e.g., saliva, blood).

Though there is considerable appeal in a validated blood test for AD pathology, most efforts to date have not been successful [15]. Recent developments, however, have shown significant promise, with high rates of overall classification accuracy [16]. If replicated and independently validated, the simplicity of a blood test would have significant clinical utility. Once integrated with the clinical history, a blood test with high sensitivity would make an excellent screening tool that could be used to quickly and efficiently rule out the presence of pathology or prompt for additional diagnostic testing.

1.4. Imaging biomarkers

Brain imaging is also a widely used biomarker, including both structural and functional imaging. For example, magnetic resonance imaging can be used to measure both regional (e.g., medial temporal structures in AD; frontal atrophy in frontotemporal dementia) and whole-brain atrophy, both of which can be used to inform differential diagnosis [17]. Several molecular imaging techniques have also been validated for detecting AD pathology (specifically β amyloid), including Pittsburgh compound B [18], and fluorine-18 labeled radiotracers such as florbetapir [19,20], florbetaben, and flutemetamol [21]. Cerebral glucose metabolism has also been widely used (e.g., fluorodeoxyglucose positron emission tomography), both for identification of early AD-related changes [22] and differentiating them from other NDDs (e.g., frontotemporal dementia) [23,24]. Tau imaging is increasingly used to identify the state of tau aggregation in the course of AD [25], which may be particularly beneficial very early in the disease process [26]. The noninvasive, or minimally invasive, nature of