An ontological representation and analysis of patient-reported and clinical outcomes for multiple sclerosis

Mark Jensen*, Alexander P. Cox, Patrick L. Ray, Barbara E. Teter, Bianca-Weinstock Guttman, Alan Ruttenberg, Alexander D. Diehl
The State University of New York at Buffalo
Buffalo, NY, USA
*mpjensen@buffalo.edu

Abstract— **We have developed the Multiple Sclerosis Patient Data Ontology (MSPD) to represent data from the patient data registry of the New York State Multiple Sclerosis Consortium (NYSMSC). MSPD is an application ontology that provides a set of classes for the annotation of both clinical measures and patient reported outcome data obtained from the enrollment forms used by the NYSMSC. To do so, we have adopted the paradigm established for representing assays in the Ontology for Biomedical Investigations. Our goal is to compare patient reported outcomes, such as self-reported disability and quality of life perceptions, to objective outcome measures in clinical practice, with reference to diagnoses and treatment modalities. We have begun an ontology-driven retrospective analysis of the patient records in the NYSMSC registry using an ontology term enrichment method in order to spot significant patterns in patient-reported and clinical outcomes in subsets of patients in the NYSMSC patient registry as compared to the NYSMSC patient population as a whole.**

Keywords—multiple sclerosis; neurological disease ontology; patient reported outcomes; OBI

I. INTRODUCTION

We have developed the Multiple Sclerosis Patient Data Ontology (MSPD)* to represent data from the patient data registry for the New York State Multiple Sclerosis Consortium (NYSMSC). MSPD is an application ontology that provides a set of classes for the annotation of both clinical measures and patient reported outcome data obtained from the enrollment forms used by the NYSMSC. Our goal is to compare patient reported outcomes, such as self-reported disability and quality of life perceptions, to objective outcome measures in clinical practice, with reference to diagnoses and treatment modalities.

A. Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) affecting over 2 million people worldwide [1]. MS pathology results in the formation of sclerotic plaques that appear in multiple regions over time throughout the CNS and are associated with a wide range of neurological symptoms [2]. MS presents clinically through varied neurological impairments such as loss of motor control and balance, weakness, sensory disturbances, and visual and cognitive deficiencies. A hallmark of MS is a heterogeneous disease course characterized by varying patterns of exacerbations in neurological impairment. Disability in MS is assessed using the Kurtzke Expanded Disability Status Scale (EDSS) [3]. In recent years a variety of new treatments have improved outcomes for many MS patients, yet the disease is considered incurable and progressive in its course.

B. New York State Multiple Sclerosis Consortium

The New York State Multiple Sclerosis Consortium (NYSMSC) is an alliance of treatment centers organized to prospectively assess clinical attributes of MS patients [4]. The NYSMSC patient registry includes data from more than 15 MS centers across New York State and is the largest clinical-based cohort of MS patients in the United States with over 10,000 registrants and 17,000 follow-up visits. It uses standardized data collection forms addressing demographic and clinical information, with an annual follow-up providing routine tracking of disease progression. The LIFEware system is used to record patients' perceptions of their physical and psychosocial impairment as a way of capturing patient reported data related to quality of life and wellbeing [5]. Clinical information collected includes: disease status, number of exacerbations, current therapies, EDSS scores, and imaging data. The data have been used for studies on the evolution of benign MS and of correlations between fatigue and depression in patients with MS [6, 7].

C. Patient Reported Outcomes

A patient reported outcome (PRO) is generally considered to be an assessment of any aspect of a patient's health status that comes directly from the patient without interpretation by a clinician [8]. PROs are a valuable tool in assessing patients' perceptions about their health and wellbeing, along with other clinical metrics, such as efficacy of treatment, disease progression, etc. [9]. Instruments for obtaining PRO provide a means for measuring treatment benefits by capturing information about patients' perceptions of both their current disability and overall health. In order to better understand the relationship between patient reported outcomes and clinical measurements, along with treatments for multiple sclerosis, it is important to see how practitioners' assessments track with patients' perceptions of their wellbeing [10].

* https://neurological-disease-ontology.googlecode.com/svn/trunk/MSPD.owl

D. Ontology for Biomedical Investigations

MSPD extends the Ontology for Biomedical Investigations (OBI), which is an integrated ontology for the description of biological and clinical investigations [11]. OBI is a domain ontology that provides a set of terms and relations to support precise annotation and querying of the kinds of data generated in biomedical investigations. It represents the design, types of analyses and assays performed, and specifications, resulting in classes such as 'assay', 'plan specification', and 'measurement datum'.

II. Methods

MSPD is an OWL2 ontology built using Protégé 4 and is being developed according to OBO Foundry principles [12]. MSPD directly imports all of OBI, and along with it the Basic Formal Ontology [13]. We import select classes from such ontologies as the Gene Ontology (GO) and Functional Model of Anatomy (FMA) via OntoFox according to MIREOT standards [14, 15]. MSPD is a corollary project to the Neurological Disease Ontology (ND) [16].

De-identified patient data from the NYSMSC patient registry were annotated with a reasoned version of MSPD. Data was handled in a HIPAA-compliant fashion per our IRB approval. Ontology terms were assigned to patients' ratings of their perceived disabilities and current affective state based upon thresholds used to determine whether responses to particular Lifeware questions merited annotation. For the results presented herein, the thresholds were set to annotate fairly stringently, in most cases at the second highest score (on scales of 1-4, 1-5, or 1-7), such that only stronger statements of disability or negative affective ratings resulted in annotation. Following annotation, subsets of patients were compared according to gender to the population of patients as a whole with determination of p-values based on the hypergeometric distribution in a way similar to that developed for term enrichment analysis for the GO [17]. The hypergeometric distribution was performed utilizing code taken from http://www.perlmonks.org/bare/?node_id=856875. Perl scripts were written to perform both the annotation and term enrichment portions of the analysis using MSPD.

III. Ontology Structure

A variety of processes are parts of the NYSMSC enrollment process. One subprocess involves the clinician preforming a comprehensive neurological examination, elements of which can be seen as assays of the patient's neurological functioning. Another part of the enrollment process includes the patient evaluating aspects of their own neurological and motor functioning, rating physical limitations, and perceived disease progression. Along with these measures, patients are asked to indicate overall life satisfaction and to what extent they are bothered by certain moods and feelings. These self-assessments qualify as PRO and correlate to standard quality of life metrics. To represent theses aspects of the enrollment process we utilized the paradigm established by OBI for representing assays.

An OBI 'assay' is defined as "a planned process with the objective to produce information about the material entity that is the evaluant, by physically examining it or its proxies" [11]. All assays specify an output, an information content entity, which is about the evaluant. In our case, the evaluant is a MS patient that is also an enrollee in the NYSMSC. More precisely, the evaluant is a Homo sapien that bears an enrollee role. For simplicity, we defined a constructed class labeled 'NYSMSC enrollee' that is equivalent to: 'Homo sapien' *and* **is bearer of** *some* 'NYSMSC enrollee role'. The role is realized during the enrollment process

Two hierarchical distinctions emerged in generalizing the types of assays present in the enrollment process for the NYSMSC data registry. One relates to distinguishing between who does the evaluating, either clinician or patient. We created two upper level classes: 'clinician reported assay' and 'patient reported assay'. A 'patient reported assay' is "an OBI assay wherein a patient produces information about themselves as the evaluant" and a 'clinician reported assay' is "an OBI assay wherein a clinician produces information about a patient as the evaluant". We further distinguish assays by what the information they produce is about. Assays are distinguished by producing data about functional impairments, such as perceived limitation with a limb, and information about affective judgments, such as being bothered by depression or pessimistic thoughts, as well as assays that produce externally verifiable facts such as date of birth and marital status.

The second hierarchy involves parthood distinctions based on the structure and composition of the enrollment forms. The 'NYSMSC enrollment form assay' represents the overall encompassing process of completing all portions of the enrollment form. It has two subparts, 'NYSMSC clinician reported enrollment assay and 'NYSMSC patient reported enrollment assay'. These in turn have multiple subparts that correspond to the numbered questions on the form, such as 'timed ambulation assay' and 'limitation assay'.

Fig. 1 illustrates some of this structure in the ontology. As a result of making these two general distinctions amongst assay types, MSPD contains an asserted subclass hierarchy of general types of assays defined by what is being assayed, which are connected through parthood relations to assays that represent the enrollment forms themselves. This way of building MSPD gives us a clear separation between types of assays based who's producing the information and what that information is about, versus the assay's place in the structure of the enrollment form, and subsequently, the enrollment process itself. Not only do we believe this to be more ontologically precise, but it allows for more robust reasoning capability.

The definition for OBI assay requires the specified output be about a material entity. In this case that entity is a patient. But, when considering how to relate the information each assay produces to what aspect of the patient is being assessed, we needed to specify more than existence of the patient. A patient bears certain qualities and functions, such as his or her visual or cerebellar function, which ultimately are the entities of interest in these assays. These functions are realized during the assay process (when successful) as the patient is being evaluated. It is these realizations (functionings) that can be observed, measured, quantified in some cases, and used in making judgments about impairment. Thus, to relate the datum

that each assay produces to the aspect of a patient's functioning being evaluated, we utilized the following guideline for creating instance-level relations in MSPD assay classes:

'OBI assay' **has specified output** *some*
('OBI measurement datum' *and* (**is about** *some*
('NYSMSC enrollee' *and*
is bearer of *some* 'BFO function')))

'OBI assay' **realizes** *some* ('BFO function'
and **inheres in** *some* 'NYSMSC enrollee')

For example, the 'vision limitation assay' refers to the part of the enrollment process wherein an enrollee is asked to rate how limited their vision is on a scale of 1 ("no limitation") to 7 ("severe"). We take the output of the assay to represent a judgment the enrollee makes about their visual functioning. We assert that every output datum from this assay is about the enrollee who is the bearer of an instance of a 'visual function'.

Likewise, the clinical reported component of the visual score in the EDSS assay, the 'EDSS visual function assay' produces a datum about the enrollee and the enrollee's visual functioning. But, it is important to connect the functions, which are borne by the enrollee, to instances of their realizations in that particular assay since the clinician is measuring these realizations. We import the GO classes for various neurological and sensory processes, thus enriching the ontological representation by connecting these assays to the apparatus that GO provides for annotation to genes and molecular functions.

'MSPD EDSS visual function assay' **realizes** *some*
('MSPD visual function' *and* **inheres in** *some*
'NYSMSC enrollee')

Fig. 1 illustrates some of the relations in MSPD.

A final structural component of the ontology relates to data analysis tasks. To give our clinical collaborators the ability to select and annotate subsets of patients based on varying and unique criteria, we developed slasses that extended 'OBI conclusion based on data', defined as "an information content entity that is inferred from data" [11]. Such conclusions are linked to their data by the OBI relation 'is supported by data'. Through this, the ontology enables user-specific instance level assertions about how certain data items support particular conclusions about disability status, quality of life metrics, and so on. For example, a conclusion that a patient has limited function in their right lower limb may be inferred based upon a score of 2 or higher (essentially any indication of limitation) in the assay wherein limitation in that limb is evaluated. Alternately, only the highest score of 4 (maximal limitation) could warrant such a conclusion in a different context.

'MSPD limitation in right lower limb conclusion'
is supported by data *some*
('OBI data item' *and* **is specified output of**
some 'MSPD right lower limb limitations assay')

An advantage of this design is that different instances of these conclusions can be created using the same datum. An assay that evaluates a patient's limb functioning produces data that can be used to support various conclusions about limitation with that particular limb. The assay itself and the datum it produces are neutral with respect to whether limitation actually exists. But, a clinician or researcher can interpret the result and then decide if it supports such a conclusion.

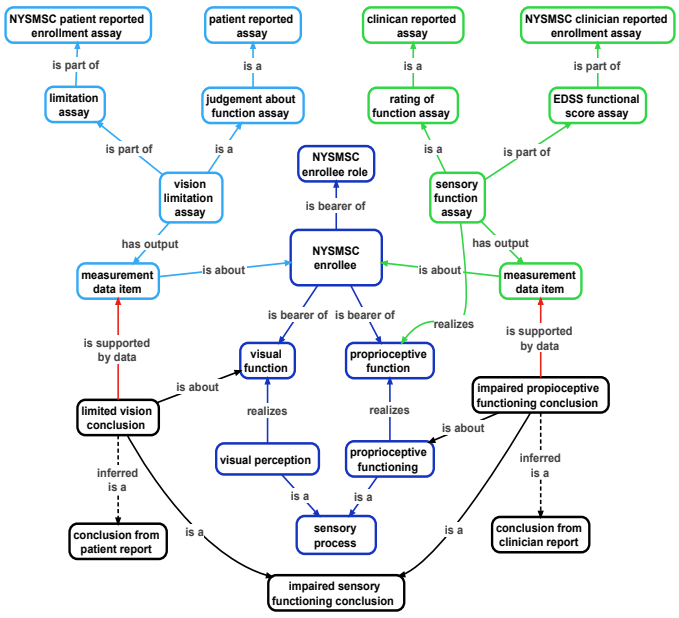

Fig. 1. A subset of classes and relations in MSPD. Except for "is a" all relations are between instances of classes.

IV. Data Analysis

We performed an analysis of 9331 patient records from the NYSMSC data registry, selecting subsets of patients based on gender, 6916 female and 2389 male. All data points for patients in each subgroup were annotated with the 'conclusion based on data' subclasses corresponding to the assays for both PRO and certain clinical measures, such as EDSS scores. We determined which data were annotated by setting a unique threshold for each particular assay output. To eliminate patient records where minimal or no disability was present, we set the threshold high. Term enrichment was performed on each annotated subset using the hypergeometric distribution method established for the GO and used successfully for term enrichment studies based on disease ontologies [17,18].

As Table 1 shows, terms related to patient reported limitations in limbs were associated with highly significant p-values for over- or under-enrichment in the results for the two cohorts. Interestingly ontology terms annotated to the male cohort were significantly over-enriched while those for the female cohort were significantly under-enriched in all terms in the ontology that related to perceived limitations in limbs. This finding suggests that the male MS population experience or report limitations in limbs at a higher rate than female MS patients do, or alternately, that female patients under report such limitations.

TABLE 1A: Male Cohort

P-value		label
1.02E-13	over-represented	limitation with limb conclusion
6.32E-13	over-represented	limited lower limb function conclusion
1.11E-10	over-represented	limitation in right limb conclusion
2.71E-10	over-represented	limitation in right lower limb conclusion
5.58E-10	over-represented	limited left limb function conclusion
1.09E-09	over-represented	limited left lower limb function conclusion
1.81E-07	over-represented	limitation in upper limb conclusion
2.28E-06	over-represented	limited left upper limb function conclusion
2.67E-03	over-represented	impaired pyramidal tract functioning conclusion

TABLE 1B: Female Cohort

P-value		label
5.44E-14	under-represented	limitation with limb conclusion
4.34E-13	under-represented	limited lower limb function conclusion
4.58E-11	under-represented	limitation in right limb conclusion
1.49E-10	under-represented	limitation in right lower limb conclusion
5.02E-10	under-represented	limited left limb function conclusion
9.01E-10	under-represented	limited left lower limb function conclusion
3.15E-07	under-represented	limitation in upper limb conclusion
4.44E-06	under-represented	limited left upper limb function conclusion
2.25E-03	under-represented	impaired pyramidal tract functioning conclusion

Table 1. The first 8 lines in each table show p-values for terms related to patient reported limitations in limbs. The last line shows the p-value for the clinical measure associated with limb limitation: the pyramidal function score component of the EDSS.

Also of interest, the conclusion based on data from the clinician reported component that most closely relates to limb functioning, the pyramidal tract functional score of the EDSS assay, showed only relatively minimal significance between each gender-based subgroup and the general population. This suggests that while male patients reported more limitation in limb functioning than female ones, the objective clinical measure of disability in MS patients did not correspond to these reports as strongly. That is to say, terms were only minimally enriched for the clinician reported measures, whereas they were highly enriched for the patient reported measures that related to limb functioning.

V. Conclusions and Future Work

Thus far we have developed an ontology for representing aspects of the enrollment process in the NYSMSC patient data registry. Specifically, we have classes for representing assay processes and the data they produce. These assays are evaluations of both patient reported and clinical measures of quality of life, disease status, neurological impairment, and functional limitations. Classes were also developed to represent different types of conclusions that could be made using the available data so that thresholds could be individually established and easily changed for analysis purposes. The data produced from the assays are used to support conclusions indicating patient-perceived or clinician-measured impairment.

We used the ontology to perform a term enrichment analysis of subsets of patient records obtained from the data registry. We discovered that ontology terms annotated to male patients in the NYSMSC registry are highly over represented for terms related to limitation in limbs versus terms annotated to female patients, even though the corresponding clinical measures were only marginally over-represented.

The preliminary results presented herein are fairly striking, and we will work with our clinical collaborators to develop interesting questions to answer via annotation of the NYSMSC patient data and application of the term enrichment methodology. We recognize that there are a myriad of ways to select and group subsets of patient records. We are particularly interested in comparing patient cohorts treated with particular drugs versus cohorts treated in other ways. Through this work we hope to gain insight into the efficacy of particular treatment regimens as measured via both patient reported and clinical outcomes.

Acknowledgments

This work was supported by a National Multiple Society Pilot Project Grant, PP1970, and by the State University of New York at Buffalo.

References

[1] NMSS. National Multiple Sclerosis Society. 2013; Available from: http://www.nationalmssociety.org.

[2] Polman, C.H., et al., Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol, 2011. 69(2)

[3] Kurtzke, J.F., Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 1983. 33(11).

[4] Jacobs, L.D., et al., A profile of multiple sclerosis: the New York State Multiple Sclerosis Consortium. Mult Scler, 1999. 5(5): p. 369-76.

[5] Baker, J.G., et al., A brief outpatient functional assessment measure: validity using Rasch measures. Am J Phys Med Rehabil, 1997. 76(1).

[6] Krupp, L.B., et al. Longitudinal correlates of fatigue in a sample of 2753 persons with multiple sclerosis. in Neurology. 2005. Lippincott Williams & Wilkins, 530 Walnut St, Philadelphia PA 19106, USA.

[7] Zivadinov, R., et al. Evolution of benign multiple sclerosis in the New York state multiple sclerosis consortium according to different classification criteria. in Multiple Sclerosis Journal. 2006. Sage Publications Ltd, 1 Olivers Yard, 55 City Road, London, England.

[8] Deshpande, P.R., et al., Patient-reported outcomes: A new era in clinical research. Perspect Clin Res, 2011. 2(4): p. 137-44.

[9] Health, U.S.D.o., et al., Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes, 2006. 4: p. 79.

[10] Benedict, R.H., et al., Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. J Neurol Sci, 2005. 231(1-2): p. 29-34

[11] Brinkman, R.R., et al., Modeling biomedical experimental processes with OBI. J Biomed Semantics, 2010. 1 Suppl 1: p. S7.

[12] Smith, B., et al., The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration. Nat Biotechnol, 2007. 25(11).

[13] Grenon, P. and B. Smith, SNAP and SPAN: Towards dynamic spatial ontology. Spatial cognition and computation, 2004. 4(1): p. 69-104.

[14] Xiang, Z., et al., OntoFox: web-based support for ontology reuse. BMC Res Notes, 2010. 3: p. 175

[15] Courtot, M., et al., MIREOT: The minimum information to reference an external ontology term. Applied Ontology, 2011. 6(1): p. 23-33..

[16] Jensen, M., et al., The neurological disease ontology. J Biomed Semantics, 2013. 4(1): p. 42.

[17] Boyle, E.I., et al., GO::TermFinder--open source software for accessing Gene Ontology information and finding significantly enriched Gene Ontology terms associated with a list of genes. Bioinformatics, 2004. 20(18): p. 3710-5.

[18] Shah, N. H., et al. Chapter 9: Analyses using disease ontologies. PLoS Comput Biol, 2012. 8(12), e1002827. doi: 10.1371/journal.pcbi.1002827