



# Real-life clinical data mining: generating hypotheses for evidence-based medicine

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*Provenance:* This is an invited article commissioned by the Editorial Office, *Annals of Translational Medicine*.

*Comment on:* Zhou ZR, Wang WW, Li Y, *et al.* In-depth mining of clinical data: the construction of clinical prediction model with R. *Ann Transl Med* 2019;7:796.

Submitted Oct 11, 2019. Accepted for publication Oct 22, 2019.

doi: 10.21037/atm.2019.10.99

View this article at: <http://dx.doi.org/10.21037/atm.2019.10.99>

Zhou *et al.* report in this journal a series of methodological reviews of clinical prediction model construction in 16 sections. They thoroughly explain the concept, current application and construction methods required to create such models with real-life data. Evidence-based medicine is based on randomized clinical trials designed to answer specific questions, like the efficacy or toxicity of a treatment. The large number of parameters that need to be taken into account to treat patients makes it very difficult to design dedicated trials (1). Clinicians need to be able to use all the data generated by a patient, in order to better personalize the therapy. Electronic health records (EHR) could be used to create detailed phenotypes. At the same time, the similarity between patients included in research protocols and “everyday” patients is questioned (2). New approaches are needed, where we can use detailed phenotypic profiles of a large number of patients in order to define new treatment strategies. Here we will develop the concepts on which predictive models are built.

## Data science and the concept of Big Data in medicine

The concept of Big Data is generally used to describe “datasets so large or complex that traditional data processing methods are inadequate” (3). The concept also relies on the definition provided by Gartner, which proposed to describe Big Data by its Volume, variety and Velocity (4). Additional “V’s” have since been used, including Veracity, Value, and

Variability (5).

## Volume: how big is Big Data?

The size of big datasets, their complexity and diversity, make them difficult to store, retrieve, manipulate and analyze. New datasets are made available every day, yielding petabytes ( $10^{15}$  bytes) or exabytes ( $10^{18}$  bytes) of data.

## Variety: where does Big Data come from?

Variables that should be considered and integrated into a Big Data analysis are heterogeneous by nature (6). They can be extracted from medical software or from electronic health records and include, but are not limited to:

- ❖ Clinical features (medical history, type, stage and grade of cancer, patient reported outcomes)
- ❖ Imaging features: number of lesions, size, volume, texture, radiomics features
- ❖ Molecular features: treatment sensitivity (7), proliferation and normal tissue reaction (8).
- ❖ Treatment features: drug dose and temporality, surgical techniques, procedure duration.

The available sources of data can be found across many levels and scales: from molecular, cellular data to whole individual or populations. This data can be either structured or unstructured. Structured data are well organized, and follow a consistent pattern. They are simple to enter, store, query and analyze. In healthcare, examples of structured

data are genomics data, laboratory tests results and data generated by treatment planning or record and verify systems. In medical specialties relying on informatics systems for treatment planning and delivery, data is already highly structured and can be easily extracted. However, this data can have very heterogeneous labels that will require time-consuming curation. On the other end of the spectrum, unstructured data has no predefined and does not conform to rows and columns. This kind of data can be extracted from various sources (medical notes, manuscripts, reports) and medical imaging (radiographs, computed tomography, and magnetic resonance imaging). Up to 80% of healthcare data is unstructured (9).

### **Velocity: how fast is Big Data generated and interpreted?**

The Velocity concept of Big Data is related to how frequently the data is updated or the data's growth over time (10). This feature is of major importance in population or public-health datasets where receiving and analyzing data in real-time could improve the understanding of a phenomenon and its mitigation. Data updated in real-time has significant value, as it could be leveraged for strategic decisions in a preventive or therapeutic manner. A system collecting a huge amount of data, but unable to analyze it rapidly would be useless in that setting.

### **Variability: how does Big Data change?**

Variability is related to the heterogeneity of the data available, its completeness and how it may change over time. Analyzing data that changes dynamically represents a significant methodological challenge: data quality control procedures must be used, with decision on how to impute missing values or how to handle repeated measurements (3). For instance, gene transcription can be different in different organs and change over time. The context in which a genomics analysis is performed can be very important for the interpretation of the results.

### **Veracity: how accurate is Big Data?**

The concept of Veracity relates to the fact that the quality of the data is very important: no matter how well the data will be used, if its quality is bad, the results will not be interpretable. Noise, redundancy, inconsistency can lead to significant bias and should be controlled before any analysis

pipeline is used. Data needs to be cleaned in a faithful manner with rigorous integrity (11) before it can be used. "Dirty Data" will provide poor results: the use of flawed, or nonsense input data will produce nonsense output or "garbage". This is the GIGO principle: "Garbage In, Garbage Out", no matter how many patients are included, or how many variables are explored.

In order to minimize this effect, EHR standardization should be favored. Data heterogeneity will lead to methodological difficulties and unreliability. In that regard, the use of standard medical ontologies in reports is almost mandatory. There are currently approximately 440 medical ontologies. The most common are SNOMED (12), the NCI Thesaurus (13), CTC AE (14) and the UMLS meta-thesaurus (15).

### **Value: why is Big Data important?**

Big Data has the potential to provide an understanding of complex conditions that rely on many different variables that have been resistant to analysis. The value also comes from the fact that it could generate new knowledge more quickly than the traditional scientific methods (16,17). Big Data is also unbiased by prior knowledge and holistic, since it is not limited to a single pathway or individual. In that sense, Big Data better captures the variability of biology or individuals (18). The size of big datasets, their complexity and diversity, make them difficult to store, retrieve, manipulate and analyze. New datasets are made available every day, yielding petabytes ( $10^{15}$  bytes) or exabytes ( $10^{18}$  bytes) of data. Today, the volume of data for an initial patient file will be around 10 GB, with genomics and imaging accounting for most of this amount.

Modelling can rely on traditional statistics or machine learning techniques. In any case, their main objective is to produce a model able to classify, predict, and estimate an outcome using known data. These models can encompass a higher number of parameters than the human can do (19). Machine Learning methods include artificial neural network, decision trees, random forest, support vector machine or bayesian networks, to name a few. One of the main limitations of the most advanced machine learning techniques lie in the fact that they are hardly interpretable.

In their article, Zhou *et al.* focus on logistic regression methods, that have the advantage to be easily interpreted and understandable by a human. They provide clear explanations on methods and hands-on examples with R code that will be very relevant for any clinician.

## Acknowledgments

None.

## Footnotes

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Bibault JE. Real-life clinical data mining: generating hypotheses for evidence-based medicine. *Ann Transl Med* 2020;8(4):69. doi: 10.21037/atm.2019.10.99