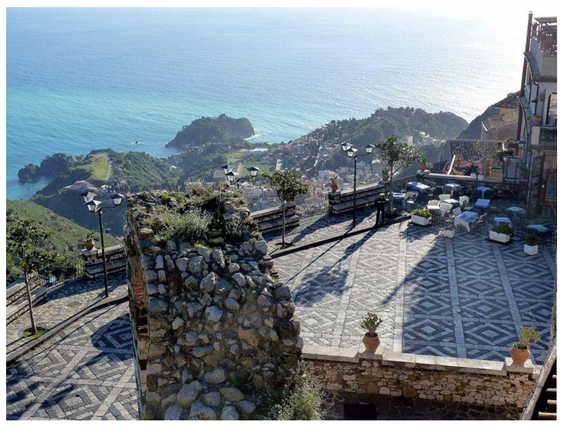

Evidence Generation for Screening and Diagnostic Tests and Algorithms

9th International Conference for EBHC Teachers and Developers
8th Conference of the International Society for EBHC
Ecosystem of evidence
Global challenges for the future
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Declaration of Conflict of Interest: Worldwide Medical Director, Women's Health & Cancer, BD Life Sciences

Background

Evidence generation for new screening or diagnostic test has traditionally emphasized a single test result, with critical statistics of sensitivity and specificity, and an ROC model for choosing a clinical cut-off. New methodologies for screening have evolved to screen-triage-triage; new methodologies for diagnosis have evolved to cascades. Single results have been replaced by algorithm determinations; some algorithms utilize advanced neural network with continuous learning capabilities. The evidence generation for an individual test that is part of screen-triage or a cascade is more complex. General screening population clinical trials have very large sample size and are exceptionally burdensome; negative predictive value requires either potentially harmful testing of screen-negative subjects to confirm ground truth, or long follow-up durations. Less burdensome evidence generation strategies and more sophisticated study designs are needed to increase value and reduce harms and waste of health research.

One approach is to utilize real world evidence (RWE). RWE is evidence regarding the usage, or potential benefits and risks of a test, derived from sources other than prospective clinical trials. RWE is the clinical evidence derived from the analysis of real world data (RWD). RWD are data relating to patient health status collected from a variety of sources, and studied retrospectively. RWD sources include EMR, claims databases, product registries, disease registries, patient-wearable devices, and patient-generated data.

Methods

The author used cervical cancer screening and management of abnormal results as an example of a field seeking less burdensome methodologies to meet diagnostic IVD regulatory requirements while reducing waste of health research, and analyzed experiences from the diagnostic industry, an FDA Advisory Panel, interactions with NMPA of China, interactions with TGA of Australia, and utilization of biobanks.

Factors promoting RWE

Explosion of Digitized Health Data

- Widespread EHR adoption
- Novel diagnostic technology: NGS, other omics, connected devices/diagnostics
- Other digital health devices and apps

Pressure on Life Science Co's to Increase Productivity and Value Delivered

- Need for higher success rates and shorter time to market in drug development
- Drive towards more targeted, personalized treatments to improve response and outcomes

Improved Computing and Analytics Capabilities

- Advancements in bioinformatics
- Scaling efficiency of cloud computing
- Development of sophisticated analytics like AI, machine learning

Rising Healthcare Costs and Value-Based Care

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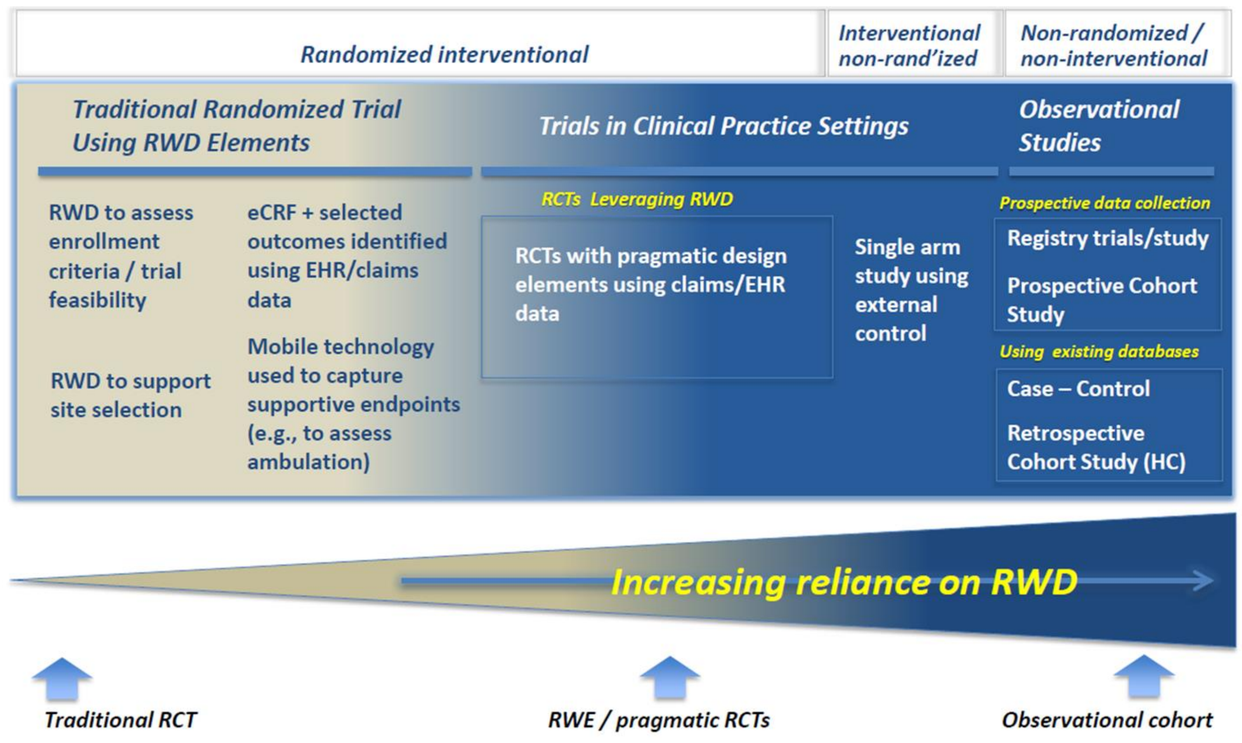
- Rising healthcare and drug costs with increased political/media attention
- Gradual implementation/ adoption of value-based care paradigms

- Increased data volume and quality
- Greater ability to derive value from this data
- Rising urgency to base product approval, coverage, treatment, and payment on real-world value

US FDA perspective on RWE



Challenges, barriers & limitations to RWE for diagnostics

- Personal health information and security concerns
- Risk of bias and methods for mitigating quality
- Study design, objectives, methodology prespecified in a formal protocol
- Missing data and methods for mitigating
- Integrating different RWD sources
- A lack of clear regulatory guidelines that will provide a framework for the collection, storage, and sharing of RWE
- Test accuracy is inherently indirect evidence for patient outcomes, resulting in default downgrading of the quality

Benefits of RWE for diagnostics

- Determine outcomes based on much larger data samples and across heterogeneous settings (general applicability)
- For filling important evidence gaps; including subjects who are under-represented in prospective clinical trials (women, minority subpopulations, pregnant women, children and adolescents, under-served)
- Understand a broader range of outcomes and patient-important outcomes than have been traditionally collected in clinical trials
- Reduce costs and improve the efficiency of clinical trials; reduce time to approval
- Utilize long-term outcomes as reference standard without requiring the duration (efficiency)
- Link data across disparate sources
- Increase personalization and precision medicine (patient-centric)
- Settings where clinical trials are impractical (rare diseases, long follow-up for endpoints, high cost)

Discussion:

Cervical cancer screening and management is changing to risk-based guidelines and reporting test results as risk predictions. These risk predictions include both incident and prevalent risks. Sensitivity and NPV are critical for the screening test; specificity and PPV are critical for the triage of positive screening test results. LR+ LR- are clinically useful when there is a cascade of screen-triage-triage; and less burdensome minimum requirements. Reductions in disease due to primary prevention (vaccination) and secondary prevention (screening) mean general screening population clinical trials would be massive; considerations for use of referral (high prevalence) populations. RWE studies require a reference standard: 'ground truth' diagnosis, but may include head-to-head with an approved test (molecular comparator).
Cervical cancer screening test regulatory standards for safety and effectiveness of a new HPV assay require 3-5 years of follow-up to determine sensitivity and negative predictive value. If the index test has already been approved, and a new use (self-sampling), or a new media (preservative) is being added, a RWE proposal may save time and money. RWE in the context requires a registry and repository. The repository must contain stored samples. The registry must contain retrospective patient health information, test results, and outcome data. The RWD must meet several criteria to be fit for purpose. The index test may be compared to the same test with a different sample type, or different media, or may be compared to another approved HPV assay (molecular comparator), as well as the clinical outcome of interest (high-grade cervical disease).
To accelerate innovation for in vitro diagnostics (IVDs) and to enable patients and health care professionals to have access to safe and effective IVD technologies, we must explore barriers, innovative methodologies, and approaches in clinical evidence generation and utilization in addition to traditional clinical studies/trials.

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