Clinical Researcher
December 2020
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Reviews and Previews of Innovations in Clinical Research

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Clinical Researcher—December 2020 (Volume 34, Issue 10)

PEER REVIEWED

Quality by Design in the RECOVERY Trial (Randomized Evaluation of COVID-19 Therapy)

Brigid Mary Flanagan, BA, RN, CCRC, MSB

If you are not following the progress of the RECOVERY trial, you should be. It is a great example of quality by design (QbD) in action. The trial is a randomized controlled study to evaluate potential treatments for COVID-19. The lead investigator is Peter Horby, Professor of Emerging Infectious Diseases and Global Health at Oxford University in the United Kingdom.

The first draft of the protocol was available on March 10, 2020. It was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the appropriate ethics committee on March 13, received regulatory approval on March 16, and received ethics approval on March 18. The first patient was enrolled on March 19, and by April 1, 1,000 patients had been enrolled. As of this writing, 15,303 participants have been randomized at 176 sites.

The trial is designed to have the least possible impact on hospital personnel. It has already demonstrated that there is no clinical benefit from the use of hydroxychloroquine in hospitalized patients with COVID-19, and that low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19.

This trial has demonstrated that when you build quality into the design of your trial, eliminate complexity, and have the buy-in of a broad spectrum of stakeholders, you can achieve success. This trial has changed clinical practice, including for pregnant women.

The Protocol

The design, conduct, and analysis of the trial is focused on issues that might have a material impact on the well-being and safety of study participants (hospitalized patients with suspected or confirmed SARS-CoV-2 infection) and reliability of results that would inform the care for future patients.{1} An additional factor to consider, in the context of this trial, is the well-being of staff, since SARs-CoV-2 is a transmissible disease.

A co-director of the study is Martin Landray, PhD, FRCP, Professor of Medicine and Epidemiology at the Nuffield Department of Population at the University of Oxford. In 2012, he argued for QbD to be factored into clinical trials whereby those responsible for the overall conduct of a trial would identify the critical aspects that, if not performed correctly, would threaten the protection of patients or the integrity of results.{2}

When developing the protocol, in early 2020, there were no approved treatments for COVID-19, the disease caused by the novel coronavirus which emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group advised that several possible treatments should be evaluated, including low-dose steroids, hydroxychloroquine, and lopinavir-ritonavir.

The inclusion criteria were unambiguous: Aged ≥ 18, admitted to hospital with proven or suspected SARs-CoV-2 infection ("suspected" infection was an early modification to the protocol). Physicians recognized the clinical syndrome, but there were delays in getting test results. They also recognized that not all tests are positive initially and that, if you are going to treat these patients, it makes sense to start treatment early, not two days later.

Eligible patients are consented by the admitting physicians. The patient is then randomized to one of several treatment arms, each of which will be given with the usual standard of care. A prescription for the assigned treatment is submitted to the hospital pharmacy, which manages supplies centrally. The main outcomes are death, discharge, the need for ventilation, and the need for renal therapy at 28 days post randomization.

It is an adaptive design trial, with the results being monitored on an ongoing basis by an independent data monitoring committee (DMC) to assess whether the randomized comparisons in the study have produced evidence that is strong enough to affect treatment strategies. Trial arms that demonstrate lack of efficacy are discontinued and new arms are added as other evidence emerges of potentially beneficial treatments. Of interest is that pregnant women are not excluded and there is no upper age limit for trial participants. The oldest participant to date has been 109 years of age.{3}

As of the end of September 2020, Version 9 of the protocol was open to enrollment. From Version 6 onwards, a factorial design (used to understand the effect of two or more independent variables) has been used so eligible and consenting participants can be randomized to one of the treatment arms in Randomization A and, simultaneously, to one of the treatment arms in Randomization B.{4} For Randomization A that can be:

i. No additional treatment
ii. Corticosteroids (pediatrics only)
iii. Azithromycin
iv. Intravenous immunoglobulin (pediatrics only)

For Randomization B, eligible patients will be randomly allocated between the following treatment arms (provided they have consented and there are no contraindications):

i. No additional treatment
ii. Convalescent plasma
iii. Synthetic neutralizing antibodies (provided by Regeneron)

Patients with progressive COVID-19 as evidenced by hypoxia (oxygen saturation < 92% on room air) and an inflammatory state (C-reactive protein (CRP)≥ 75mg/L) can be randomized a second time to either:

i. No additional treatment
ii. Tocilizumab

The larger the numbers randomized, the more accurate the results will be. Tellingly, enrollment slowed down in the summer of 2020 as the numbers of patients being hospitalized decreased. Enrollment has picked up in September and October, as the number of infections began to resurge across the UK.

Trial Processes

In line with QbD principles, all trial processes have been greatly simplified to minimize the burden on frontline staff in busy hospital settings who have been stretched to the limit during the pandemic. The University of Oxford is the trial sponsor, with trial coordination coming from a Central Coordinating Office (CCO) staffed by members of two registered clinical trial units. The CCO oversees regional coordinating centers which, in turn, assist with the selection of local centers. The study is conducted at multiple hospitals within the local regions.{4}

The consent for participation is less than five pages long and is available in multiple languages reflecting the diversity of the UK population (e.g., Polish, Urdu, Bengali, etc.). Training is all available online and must be completed before a site is activated. Training requirements are dependent on one's role in the study; for example, all are required to complete background training and those obtaining consent and/or performing randomization have additional training modules for those duties.

A one-page case report form (CRF) is completed online prior to randomizing a subject. A second CRF is completed at death, discharge, or at 28 days, whichever comes soonest. Information collected includes:

- Vital status
- Hospitalization status
- SARS-CoV-2 result
- Use of ventilation (number of days and type)
- Use of renal dialysis or hemofiltration
- Documented new major cardiac arrythmias
- Use of any medications in the RECOVERY trial or other purported COVID-19 treatments (e.g., remdesivir)

Additional information is collected in the first 72 hours for the first 200 subjects randomized in Main Randomization B (no additional treatment vs. convalescent plasma and no additional treatment vs. synthetic neutralizing antibody):

- Sudden worsening of respiratory status
- Severe allergic reaction or other infusion reaction
- Temperature >39C or ≥2C above baseline
- Sudden hypotension
- Clinical hemolysis
- Thrombotic event

In addition, Serious Hazard of Transfusion (SHOT) reporting is conducted for all patients receiving convalescent plasma for the full duration of the study. All the information collected for the study is in the medical record and would routinely be documented absent trial participation.

For data and safety monitoring, the focus is on events that, based on a single case study, are highly likely to be related to the study medication (e.g., anaphylaxis, Stevens-Johnson syndrome, or bone marrow failure), where there is no other plausible explanation. Events that are the consequence of COVID-19 and common events which are the consequence of conditions which existed prior to randomization are exempt from reporting.

Monitoring is done remotely by the CCO. Onsite monitoring will only be considered if a training need is identified or the results of central statistical monitoring suggest there might an issue. No routine source data verification is taking place. Given that there is pandemic, site visits would not be appropriate, as they could increase the risk of spreading infection.{4}

The protocol, the informed consent, sample CRF pages, training materials, and patient information sheets are all available for public viewing on the RECOVERY website at www.recoverytrial.net.

The Stakeholders

The effort to date reflects the strong collaboration among the various stakeholders. These include the National Health System (NHS), the MHRA, the ethics committee, the Health Research Authority, and the Chief Medical Officers of England, Wales, Scotland, and Northern Ireland,

who wrote to all physicians across the UK requesting their support with enrollment and encouraging a default position where every eligible patient is offered enrollment in a clinical trial.

Strong evidence requires large numbers (e.g., 2,000 subjects per arm).{5} The lead investigator had hoped to enroll 1,000 subjects a week, but that has not always been possible. However, the strong national (and international) coverage, as well as the recruitment successes to date, have resulted in requests for inclusion from other national health authorities; discussions are ongoing with Vietnam, Indonesia, and Nepal.

The aforementioned website has a section dedicated to patients. There is a video in which the co-investigators for the study describe each of the drugs being investigated as possible treatments for COVID-19 and a list of frequently asked questions.

Results to Date

The most consequential results to date have been that low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 and one fifth in other patients receiving oxygen alone. A press release issued in June 2020 indicated that 2,104 patients randomized to receive dexamethasone 6mg once a day, either by mouth or intravenously, were compared to 4,321 randomized to usual care alone. In the press release, co-investigator Landray said: “Since the appearance of COVID-19 six months ago, the search has been on for treatments that can improve survival, particularly in the sickest patients. These preliminary results from the RECOVERY trial are very clear—dexamethasone reduces the risk of death among patients with severe respiratory complications. COVID-19 is a global disease—it is fantastic that the first treatment demonstrated to reduce mortality is one that is instantly available and affordable worldwide.”{6} The trial results were subsequently published in *New England Journal of Medicine (NEJM)* on July 20, 2020.

The independent DMC concluded that there was no beneficial effect of hydroxychloroquine in patients hospitalized with COVID-19. A separate June 2020 press release {7} indicated 1,542 patients randomized to hydroxychloroquine were compared to 3,132 randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality and no

evidence of beneficial effects on duration of hospital stay or other outcomes. Those results were subsequently published in the *NEJM* on October 8, 2020. The conclusion was the same for the lopinavir-ritonavir arm, and that arm was discontinued. Those results were published in *The Lancet* on October 5, 2020.

Discussion

The RECOVERY trial is a great example of what can be accomplished when you have buy-in from all stakeholders. There is no negotiation on the contract, no payments to investigators, and no recruitment targets.{8} Indemnity is addressed in the protocol (the university has a specialist insurance policy in place which will operate in the event of any participant suffering harm because of their study participation).

The protocol objectives are clear; the primary objective is to estimate the effects of study treatment on all-cause mortality within 28 days of randomization. The secondary objectives are to investigate the effect of study treatments on the duration of the hospital stay, the need (and duration) of ventilation, and the need for renal replacement therapy. There are no tertiary or exploratory endpoints. Trial procedures are greatly streamlined, and randomization is done online. The confirmation of the allocated treatment can be downloaded and printed. Data entry is minimal. Follow-up information is collected at one timepoint only (Day 28) and can be done by phone, in person, or electronically.

Usually in studies, participants are assigned a study number and the trial sponsor does not know their identities. In this case, the participant's NHS number is collected along with some other personal details. The informed consent explicitly states that the researchers may request additional medical information that is maintained in local or national records for up to 10 years following the scheduled follow-up period. As the long-term sequelae of COVID-19 are unknown now (10 months into the worldwide pandemic), and eligible participants may be receiving investigational agents, this reservoir of data could potentially be a great source of information. This is one of the benefits of a national healthcare system.

Other points of interest are the very broad inclusion/exclusion criteria. It is refreshing to see that participants are not excluded because their body weight exceeds 30kg/m², they are pregnant, or

they are more than 65 years of age. With respect to co-morbidities, if, in the opinion of the investigator, study participation would put the patient at significant risk, they should be excluded. As the trial is for hospitalized patients and there are no known cures, participation in the RECOVERY trial may be a patient's best option for making a good recovery.

Conclusion

The RECOVERY trial is a great example of QbD in action. For people who struggle with the concept of QbD, this is an opportunity to learn from one of the original proponents for QbD in clinical trials, Professor Martin Landray. All the materials are available for access by the public, including the protocol, informed consent, patient information materials, sample CRF pages, and the statistical analysis plan. This transparency is to be commended.

The protocol is easily understood (33 pages in total). The informed consent is short and to the point. Trial processes have been simplified. Data collection is minimal. The numbers enrolled will depend on the duration of the pandemic. A DMC is reviewing the data on an ongoing basis to determine the effect of treatments on mortality that is strong enough to affect clinical practice. Most importantly, the RECOVERY trial has broad support from all a variety of stakeholders, including the MHRA and NHS clinicians, in the UK.

To date, dexamethasone (first made in 1957, off-patent and widely available around the world) is the only treatment identified to have benefits for patients receiving respiratory support. Those results have changed the management of hospitalized patients worldwide.

As research professionals, we can all learn something from this trial. The pandemic has been a catalyst for change in how trials are conducted. Let us hope we can keep that momentum going forward.

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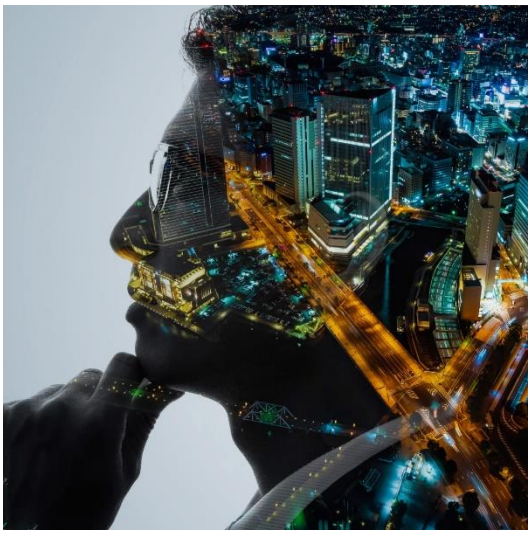
Clinical Researcher—December 2020 (Volume 34, Issue 10)

GOOD MANAGEMENT PRACTICE

Why the Future of Diagnostics Requires a New Approach to Trials

David Messina, PhD



Scientific and medical research is an investment in our future. We're all keen to live long, healthy lives and most of us are willing to empower physicians to make educated decisions about our care if and when we do become ill. Further, as we've seen from hundreds of years of scientific advancement, medicine is not a short-term investment. When a new drug or medical device comes to market, it builds on decades of basic science research, translational research and development, and clinical studies.

In the early 2000s, economists evaluated federal investments in medical and health research and found "that the returns from the national investment in medical research—both in the past and what is likely to be delivered in the future—are exceptional and far greater than is appreciated by either policy makers or the public." That said, public and private investors alike know there is no fast-track to success; no magic pathway that results in breakthroughs faster or more often.

Scientific and medical research is rigorous, methodical, and fraught with failure. Often, however, these failures come with great learning opportunities, which help yield future successes.

Learning from Clinical Studies

One such learning opportunity is centered on the clinical studies that help move therapeutics and diagnostics out of the research lab and into clinical practice. Drug trials have exploded in the last decade, particularly in immune oncology, with more than 1,000 trials initiated in the U.S. alone

last year, according to Kantar Health. This has spurred significant innovation in the therapies available for patients.

However, as we enter an era of more precise medicine, many of the therapies being developed work only in a subset of the patient population. This means there is a need for the development of a diagnostic approach for selecting patient populations who will respond well to the therapy.

At first, the industry prioritized this at the same time as the drug, developing the companion diagnostic in parallel and resulting in an on-label test that is required for safe use of the drug. An example of this is the use of a PD-L1 immunohistochemistry (IHC) assay to select patients for anti-PD-1 immunotherapies. While the intent behind this approach is sound, I would argue that it has unintentionally laid the foundation for a lack of innovation in diagnostic development.

For example, in some indications where PD-L1 IHC is currently the approved companion diagnostic device, such as recurrent and metastatic squamous cell carcinoma of the head and neck, clinicians have little to no confidence in its ability to predict response. So, rather than guiding treatment decisions, it's seen as necessary but unproductive.

Despite broad awareness of this situation, the industry has overwhelmingly focused on expanding the indications approved for treatment with anti-PD-1 therapies, and has not given sufficient consideration to improving our ability to predict response and replacing the on-label diagnostic. So it is that, as with many other facets of medical research, our failures have taught us that there is room to improve. The future of diagnostics requires a new trial approach—particularly in oncology.

Driven by Innovation

While IHC has provided decades of invaluable information, it is far from being the most sensitive or specific methodology we have at our disposal. Further, the reproducibility of the technology poses major challenges, as was evaluated in the Blueprint Study. So, when we design clinical studies—either for companion diagnostics or independent diagnostics—I would argue we should be driven by the most innovative, informative tools we have, not just what has worked well in the past and represents a "safe bet."

There are many other technologies available that have demonstrated they can generate valuable biological insights for oncology biomarkers. By moving these from the research space and into our suite of options for diagnostic development, we are expanding our arsenal in our fight against cancer. Further, when we look to more advanced technologies, we have the benefit of moving from a single-analyte snapshot to a more multidimensional, multi-analyte approach, which provides a more holistic view of the patient's disease.

Examples of other technologies that should be considered include other imaging technologies with improved sensitivity and specificity, namely, immunofluorescence and mass cytometry. If spatial information is not biologically relevant to the biomarker to be measured, then technologies using next-generation sequencing (NGS) or polymerase chain reaction (PCR) are an excellent option. This umbrella is vast and covers DNA measurements such as tumor mutational burden (TMB) and microsatellite instability (MSI), as well as RNA measurements including gene expression, immune profiling, and predictive immune modeling.

Each of these have plentiful translational research that demonstrates their potential use as oncology biomarkers, and should be considered for diagnostic development in both the companion and predictive diagnostic setting. Examples include TMB across multiple solid tumor types, co-testing MSI by PCR and dMMR by IHC, and the relationships between MSI, TMB, and PD-1/PD-L1 expression.

With the goal of precision medicine comes the need for multidimensional technologies. In the immunotherapy example, measuring holistic immune response at the site of the solid tumor is paramount to improving our ability to predict tumor response and has been shown to perform better than IHC alone. The future of diagnostic trials must leverage innovative technologies that can provide better insight into the complex biology of each patient.

Decentralized, Yet Harmonized

Diagnostic clinical studies are challenged by the same barriers to success that have been described for all clinical trials, including recruiting sufficient diversity in cohorts to represent the general patient population, ensuring compliance of patients, and confirming sites are following protocols identically. It's certainly clear that decentralized trials are most effective for recruiting

a more diverse patient population, but you might be concerned that this approach increases the latter challenge of site management.

In fact, each of the barriers listed can be reduced when a sponsor partners with a contract research organization (CRO) that is well-versed in running highly virtual trials. These CROs are equipped with platforms to provide remote monitoring, electronic patient consenting, and electronic data capture. This model even enables individual investigators, who may be passionate about science and improving patient outcomes but are not located in academic institutions with dedicated clinical trial staff, to enroll patients for participation in a clinical trial.

A virtual trial platform also allows for sponsors to leverage direct-to-patient engagement. By extending trial sites beyond large academic centers to sites local to patients, we enable maximal diversity in recruitment, streamline participant engagement, and help ensure improvements to patient compliance. This approach to diagnostic trials, especially those that are non-interventional and may not require additional hospital visits, would allow patients to participate in a clinical trial no matter where they live, what their socioeconomic status is, and who their treating physician is.

The future of diagnostic trials must be decentralized and supported by CRO partners who can keep sites and protocols harmonized.

Independent and Equally Impactful

Building a diagnostic that improves patients' care paths and clinical outcomes should not be considered an afterthought, or only considered when bringing a new drug to market. Lessons learned during the development of predictive diagnostics for new therapies demonstrate that this approach has value for all therapies available. By developing predictive diagnostics for decision points along multiple care paths rather than for only one therapy, we move closer to the precision medicine paradigm where these technologies will empower physicians to understand the potential outcomes for the myriad of therapeutic options available to them.

Robust clinical studies for biomarkers should be prioritized not only during drug development, but also for therapies already on the market. The diagnostics being evaluated for predicting

tumor response to anti-PD-1 therapy represent great progress post-therapy approval. However, we should not stop with building diagnostics for immunotherapies alone. Helping physicians make decisions about chemotherapy, radiation therapy, and combination therapies using diagnostic tools will not only improve patient outcomes, but will provide financial advantages for payers, patients, and the entire healthcare ecosystem.

Conclusion

As members of the clinical research community, we're all aware that the stakes of our investment in medical and healthcare research have never been higher. Scrutiny in how funds are spent, the rising cost of healthcare, and our aging population require us to find new ways of rising to meet these challenges.

A fixation on novel therapies alone will not allow us to meet our goals of matching patients with the most impactful treatment regimen. Expanding our efforts to focus on diagnostic innovation, and even on how and when we conduct the clinical studies that bring diagnostic technologies to market, is essential to delivering successful outcomes and closing the precision medicine gap.

David Messina, PhD, has spent the last 20 years in computational biology and human genetics. He contributed to the Human Genome Project at Washington University in Saint Louis, mapped disease genes at the University of Chicago, and co-developed the first comprehensive atlas of human transcription factor genes. As COO of Cofactor Genomics, he is the lead on all regulatory and reimbursement efforts for the company, driving the implementation of RNA-based diagnostics and their clinical application.

CLINICAL RESEARCHER

DECEMBER 2020 HOME STUDY

Reviews and Previews of Innovations in Clinical Research

Article 1—**Quality by Design in the RECOVERY Trial (Randomized Evaluation of COVID-19 Therapy)**

LEARNING OBJECTIVE

After reading this article, the participant should be able to summarize the design and goals of the RECOVERY trial, and to outline the application of the tenets of quality by design to its conduct.

DISCLOSURE

Brigid Mary Flanagan, BA, RN, CCRC, MSB: *Nothing to disclose*

1. What has the RECOVERY trial demonstrated in terms of treating hospitalized COVID-19 patients with hydroxychloroqine?

A. Superior clinical benefit.
B. Moderate clinical benefit.
C. Mild clinical benefit.
D. No clinical benefit.

2. Who did RECOVERY trial co-director Martin Landry argue should factor quality by design (QbD) into clinical trials?

A. Study sponsors responsible for bankrolling trials.
B. Participants in studies who have given informed consent.
C. Those responsible for the overall trial conduct.
D. Unbiased institutional review board members.

3. What does the RECOVERY trial's adaptive design mean?

A. Trial arms are added or discontinued based on ongoing data monitoring.
B. The trial's goals and procedures were adapted from an earlier study.
C. Trial participants may be treated with multiple therapies simultaneously.
D. The goalposts for trial endpoints may be moved at any time.

4. What has been done about the RECOVERY trial's processes in consideration of the workloads of frontline health professionals during the COVID-19 crisis?

A. They have been made strictly optional.
B. They have been greatly simplified.
C. They have been vetted by an independent data monitoring committee.
D. They have been assigned randomly to a variety of study team members.

5. Which of the following events would trigger a second case report form (CRF) in the RECOVERY trial?

A. The patient is discovered to be non-compliant.
B. The patient is randomized to placebo.
C. The patient is discharged from the hospital.
D. The patient asks for a second opinion.

6. Who monitors the RECOVERY trial?

A. The Medicines and Healthcare products Regulatory Agency.
B. The University of Oxford Independent Ethics Committee.
C. An anonymous Contract Research Organization.
D. The Central Coordinating Office of the sponsor.

7. Who wrote to physicians across the UK requesting support for the RECOVERY trial?

A. The Chief Medical Officers of England, Wales, Scotland, and Northern Ireland.
B. The University of Oxford's Clinical Trials Units.
C. The European Commission's European Health Union.
D. The U.S. Food and Drug Administration.

8. The RECOVERY trial found which readily available and affordable medicine effective at reducing the risk of death among COVID-19 patients with severe respiratory complications?

A. Penicillin
B. Dexamethasone
C. Chloroquine
D. Aspirin

9. Which of the following is a secondary objective investigated in the RECOVERY trial?

A. Effect of randomization on patient mood and satisfaction.
B. Effect of quality by design (QbD) on investigator oversight.
C. Effect of study treatment on duration of hospital stay.
D. Effect of sponsor support on monitoring efficiency.

10. How long after the scheduled follow-up period may additional medical information requested of patients by RECOVERY trial researchers be held in local or national records?

A. Up to 5 years.
B. Up to 10 years.
C. Up to 15 years.
D. Up to 20 years.

Article 2—**Why the Future of Diagnostics Requires a New Approach to Trials**

LEARNING OBJECTIVE

After reading the article, the participant should be able to describe factors influencing the need for the development of a diagnostic approach for selecting patient populations who will respond well to new therapies.

DISCLOSURES

David Messina, PhD: *Nothing to disclose*

11. An early-2000s evaluation of federal investments in medical and health research found which of the following to be true?

A. The returns had steadily decreased following the World War II era.
B. The returns could easily be doubled with modest levels of corporate taxation.
C. The returns are far greater than is appreciated by policy makers and the public.
D. The returns are likely to stagnate to a significant degree by the mid-2000s.

12. Which of the following does the author cite as a driver for developing a diagnostic approach to select patient populations who will respond well to new therapies?

A. Regulatory authorities
B. Economic incentives
C. Precision medicine
D. Ethics committees

13. What does the author say has unintentionally led to lack of innovation in diagnostic development?

A. Developing a drug and its companion diagnostic in parallel.
B. Increased competition between developers of similar products.
C. Regulatory pressure to develop breakthrough therapies.
D. Growing consumer backlash to the cost of diagnostics.

14. What does the author criticize in the case of anti-PD-1 therapies?

A. No diagnostic has ever been successful for them.
B. Their on-label diagnostic has not been replaced.
C. Diagnostics for the associated condition are too costly.
D. Regulators have discouraged diagnostics for them.

15. What does the author say should drive clinical studies of diagnostics?

A. Potential for profits from their sale.
B. Demands from patient advocacy groups.
C. Availability of suitable participants.
D. Innovative and informative tools.

16. What advanced technology is cited as providing a more holistic view of a patient's disease in oncology?

A. CRISPR gene editing
B. Immunotherapy
C. Multi-analyte approach
D. Telemedicine

17. Which of the following is cited by the author as being involved in technology with potential use as an oncology biomarker?

A. Polymerase chain reaction
B. Biorhythm measurement
C. Sleep studies
D. Alternative medicines

18. What does the author say can help a diagnostic developer reduce barriers to running virtual trials?

A. Requesting regulatory permission to conduct smaller studies.
B. Partnering with an experienced contract research organization.
C. Compensating participants at higher rates than normal.
D. Extending studies across longer lifecycles to ease cash flow.

19. The author cites which of the following as a good reason to conduct virtual trials for diagnostics?

A. Sponsors do not have to monitor patient compliance in virtual trials.
B. Regulators are much more lenient in their guidances for virtual trials.
C. Virtual trials can enable maximal diversity in patient recruitment.
D. Virtual trials can easily be repeated at no extra cost if needed.

20. What does the author say can be done with predictive diagnostics to move closer to the precision medicine paradigm?

A. Develop them to be more widely accepted by insurance plans.
B. Develop them to be proven effective with as few participants as possible.
C. Develop them for use only in the most life-threatening diseases.
D. Develop them for decision points along multiple care paths.