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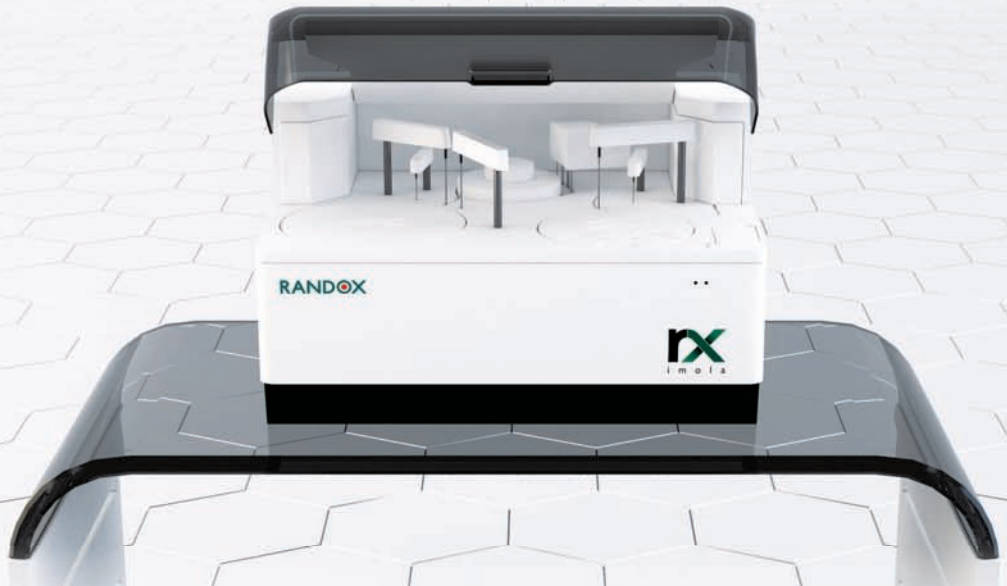

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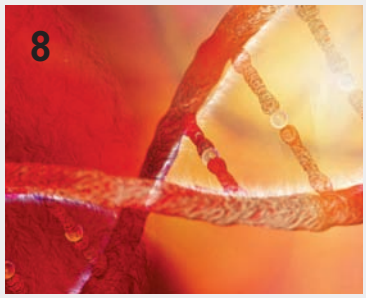

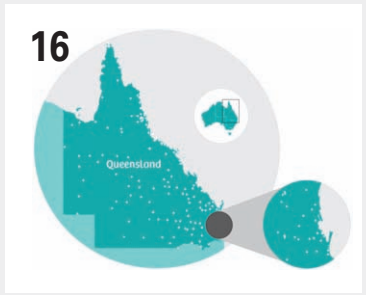

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Calling all Moynihans

By Lisa Moynihan
Editor

Moynihan is my maiden name. I don't know much about my genealogy but this is what I've been told: (a) my father is Irish. (Moynihan); (b) my fraternal grandmother was Irish. (MacGuire); (c) my mother is English. (Mason); (d) my maternal grandmother was German. (Schneegold); and (e) there are no more male Moynihans (in my immediate family) to pass on the Moynihan name.

I'll know more in six to eight weeks, when my AncestryDNA results come back.

Parents and children share 50 percent of their DNA with one another. Therefore, testing my parents will help deduce which of my own ethnicities and DNA matches come from which parent. So, for Christmas I gave each parent a kit. Neither were tap dancing over the idea, but each are willing to participate.

Coincidentally, our Christmas Eve family convo was thick in the topic of DNA testing. Just days prior, a local news story reported a man's arrest and conviction for a 20-year-old murder, traced back to one of his family member's DNA. Surprisingly, my in-laws personally knew this murderer, and opinions started flying! "Oh, heck no!" "No one is going to clone me!" "There's no telling who will get ahold of it!" "Big Brother won't be watching me!" And so down the rabbit hole the conversation went.

I just opened my kit today. I learned some new things, like the kit expires after one year of purchase and samples aren't taken via mouth swab, but a vial for spit, along with a liquid solution that stabilizes the DNA in the saliva. What it didn't tell me was where my saliva will be tested. A "DNA Processing Lab" is all I could find. However, after further research, I learned AncestryDNA samples have been outsourced to Quest Diagnostics' 200,000 square foot reference lab in Marlborough, MA since 2017.[1]

Knowing that all Quest Diagnostics' testing locations are appropriately licensed/certified by CLIA 88 and adhere to state laboratory licensure programs gave me more confidence—as we all know, accuracy is dependent on the quality of the laboratory's testing procedures. The collaboration between Ancestry and Quest is a great example of a company relying on clinical diagnostic labs to perform services for its customers. It also illustrates the need for clinicians and laboratory professionals to remain current on industry trends in ways that might help their labs to increase profit and provide value-added services to consumers.

A similar image (shown below) was taken by *MLO* Publisher/Executive Editor, Kristine Russell, and emailed to me when she was in Cork, Ireland a few years ago. Who knows…perhaps this was the seed that initially ignited my genomic curiosity? I really do want to learn more about who I am as an individual and how I connect to the world around me. Especially if it means chickens are in my future!

Image courtesy of: http://www.englishmarket.ie/traders/poultry/moynihanspoultry/

REFERENCE

1. Quest Diagnostics and AncestryDNA Collaborate to Expand Consumer DNA Testing. PR Newswire. https://www.prnewswire.com/news-releases/quest-diagnostics-and-ancestrydna-collaborate-to-expand-consumer-dna-testing-300308333.html. Accessed Jan. 10, 2019.

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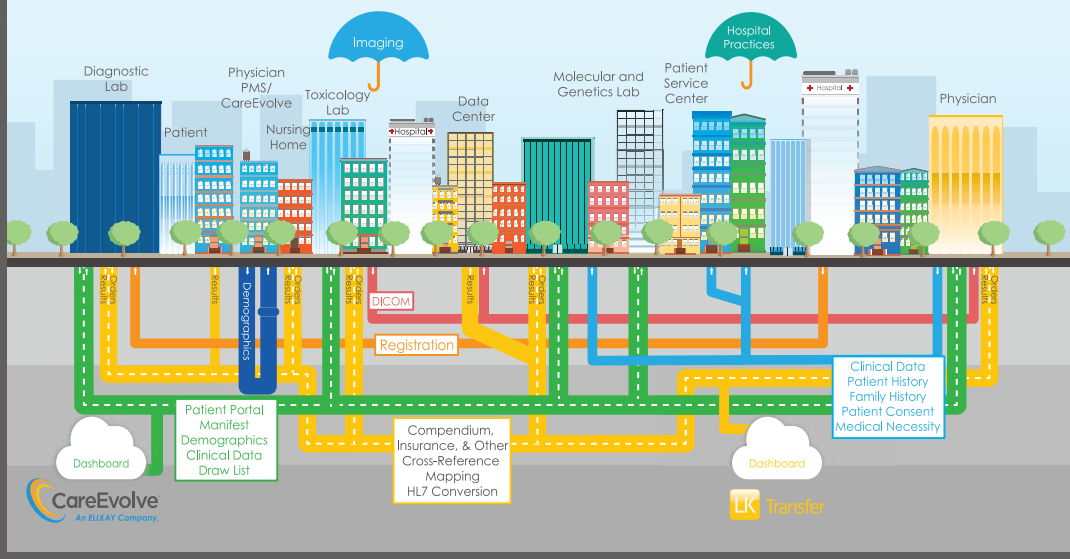

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FAST FACTS

Cervical Cancer

Here are some interesting numbers about cervical cancer. Virtually all cases of cervical cancer are caused by specific types of human papillomavirus (HPV).

13,240

is the approximate number of new cases of invasive cervical cancer diagnosed in the U.S. in 2018.

4,170

is the estimated number of women to have died in the U.S. from cervical cancer in 2018.

35-44 years

is the age range at which cervical cancer is most frequently diagnosed.

15 percent

or more cases of cervical cancer are found in women over age 65.

9 out of 10

cervical cancers are squamous cell carcinomas.

21 years

is the recommended age to start getting Pap tests.

70 percent

of cervical cancers worldwide are caused by HPV-16 and HPV-18.

80 percent

of cervical cancer cases occur in developing nations.

75 percent

is about the 5-year relative survival rate for women diagnosed with cervical cancer.

Sources:
https://www.cancer.org/cancer/cervical-cancer/about.html, https://www.cdc.gov/cancer/cervical/index.htm, https://report.nih.gov/nihfactsheets/viewfactsheet.aspx?csid=76

HPV

HPV discovery raises hope for new cervical cancer treatments. Researchers at the University of Virginia (UVA) School of Medicine have made a discovery about human papillomavirus (HPV) that could lead to new treatments for cervical cancer and other cancers caused by the virus.

HPV is responsible for nearly all cases of cervical cancer and 95 percent of anal cancers. It is the most common sexually transmitted disease, infecting more than 79 million Americans. Most have no idea that are infected or that they could be spreading it.

HPV has been a stubborn foe for scientists, even though researchers have a solid grasp of how it causes cancer: by producing proteins that shut down healthy cells' natural ability to prevent tumors. Blocking one of those proteins, called oncoprotein E6, seemed like an obvious solution, but decades of attempts to do so have proved unsuccessful.

UVA researcher Anindya Dutta, PhD, of the UVA Cancer Center and his colleagues, however, have found a new way forward. They have determined that the virus takes the help of a protein present in our cells, an enzyme called USP46, which becomes essential for HPV-induced tumor formation and growth. And USP46 enzyme promises to be very susceptible to drugs.

"It's an enzyme, and because it's an enzyme, it has a small pocket essential for its activity, and because drug companies are very good at producing small chemicals that will jam that pocket and make enzymes like USP46 inactive," said Dutta. "So, we are very excited by this possibility that by inactivating USP46 we'll have a way to treat HPV-caused cancers."

Curiously, HPV uses USP46 for an activity that is opposite to what the oncoprotein E6 was known to do. E6 has been known for more than two decades to recruit another cellular enzyme to degrade the cell's tumor suppressor, while Dutta's new finding shows that E6 uses USP46 to stabilize other cellular proteins and prevent them from being degraded. Both activities of E6 are critical to the growth of cancer.

The researchers note that enzyme USP46 is specific to HPV strains that cause cancer. It is not used by other strains of HPV that do not cause cancer, they report.

UDT

Urine drug testing may be important in early phases of addiction treatment. A new study performed by Boston Medical Center and faculty at the Boston University School of Medicine shows that urine drug testing (UDT) can be a useful tool to treat patients with opioid use disorder in a primary care setting.

The analysis revealed that patients are less likely to disclose drug use earlier in treatment, and although the study was not able to identify reasons for this, the authors believe that it may be related to fear of discharge from a treatment program and stigma related to relapse.

Published in *Drug and Alcohol Dependence,* the study indicates the need to develop interventions for patients who have positive UDTs urine drug tests in order to keep them engaged in care.

The researchers correlated the frequency of patients' self-reported substance use and the results of their UDTs. It showed that 76 percent of UDTs positive for cocaine and 57 percent of those positive for opioids occurred when patients did not disclose substance use in their treatment visit. Additionally, rates of positive UDTs without self-reported substance use were higher earlier in treatment, possibly reflecting growing trust between the patient and the treatment team over time.

Overall, the study reinforces the current guidelines that call for using UDTs to monitor for substance use in office-based addiction treatment but encourage less frequent testing as patients become stable in their recovery.

Correction

Regarding the January 2019 CE Test, page 10: question number 16 was printed incorrectly. The correct version is now available at https://www.mlo-online.com/wp-content/uploads/2018/12/MLO-201901CEtest.pdf. We apologize for the error.

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It's all in the genes—expanding molecular testing to improve healthcare for those with blood disorders

By Jerry A. Holmberg, PhD

Information the genes impart on man's characteristics including future disease conditions has not been always understood. Friedrich Miecher, a Swiss Chemist, was the first to expand man's knowledge of nucleic acid in the 1860's; however, Watson and Crick greatly improved our understanding of deoxyribonucleic acid (DNA) over 60 years ago. Since then the genes that control the sequence of DNA and the role of ribonucleic acid (RNA), as well as the products of the molecular codes, continues to be clarified. Molecular testing has moved from the research laboratory to the clinical laboratory. This transition has enabled science to gain insight into genetic differences, mutations (ie: Huntington Disease, Down's syndrome, Philadelphia chromosome), diseases, cell growth, cancer onset, and blood disorders; moving medical science to a new frontier.

The part of the gene that codes for amino acids responsible for protein structure is referred to as an exon. These protein products are biomarkers which can appear in the plasma or on cell surface to indicate normal or abnormal cellular function. Expanding our understanding of these biomarkers has been extremely beneficial in diagnosis and management of various disease states and avoiding adverse events.

Modern medicine has harnessed molecularly determined biomarkers to manage various disease states. The recent 2018 Nobel Prize award in Physiology or Medicine highlighted this. Drs James P. Allison and Tasuku Honjo were honored for advancing cancer treatment by using the host's immune system to arrest or limit cancer. Honjo's discovery of Program Cell Death-1 (PD-1) has been effective in treating lung cancer, renal cancer, lymphoma, and melanoma.

Earning CEUs

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Recall the history of the discovery and findings of the ABO and Rh blood group systems and discuss the evolution of molecular testing into the immunohematology lab.
2. Explain the differences of phenotype versus genotype testing and discuss phenotype testing limitations.
3. Discuss the advantages that genotype testing offers in certain disease states and weak D individuals.
4. Recall the molecular tests for blood group genotyping that are current on the market and discuss their differences.

Blood groups are biodeterminants

So, what about using molecular testing for blood disorders? In the clinical laboratory, the blood bank has been at the forefront of routinely testing for biomarker determinants either through the antigens formed by genetic uniqueness of the patient or the immune response to those biomarker determinants. In the early 1900s, Karl Landsteiner was the first to demonstrate the phenotypic differences of the blood group system, later known as the ABO blood group system. The ABO system continues to be the most important blood group system with antigens expressed on red cells, platelets, and other tissues. At the time of Landsteiner's description of the ABO system, he did not know that these observed differences were gene-controlled glycoproteins with specific carbohydrates (sugars) forming immunodominant carbohydrate epitopes. The ABO system is controlled by the ABO gene and another precursor gene (H gene), responsible for the H antigen. When the H antigen is present, and depending on the presence or absence of A and B glycotransferase, N-acetylgalactosamine (GalNAc) will form the A antigen or Galactose (Gal) will form the B antigen or no additional sugar will be added to the H antigen for a phenotype of group O. If the H antigen is absent, the red cells are of the very rare Bombay phenotype.

Although the mechanism is not fully understood, there appears to be a relationship between the ABO and other carbohydrate blood group systems with malignancy, cellular adhesion, and some infectious disease.[1,2] West Nile Virus and Zika Virus have been associated with the red cells and may adhere throughout the erythrocytes' lifespan.[3,4]

Next to the ABO system, the Rh system, and the Kell system, are blood group systems of clinical significance in transfusion practice. In 1939, Levine and Stetson observed that the serum of a pregnant woman agglutinated 80 percent of ABO compatible samples, resulting in the identification of the Rh blood group system. The Kell system was the first system identified following Coombs technique, which uses anti-human globulin to detect antibodies adhered to the red cells. To date, the field of immunohematology has identified 54 antigens associated with the Rh system and 36 antigens in the Kell system. Unfortunately, many of these discoveries have been associated with adverse events in women of child bearing age and those individuals with chronic transfusion dependent diseases.

What is observed is not necessarily what is encoded in the genes. The phenotype is the observed characteristics of the gene. In the clinical immunohematology laboratory, the observed characteristics (phenotype), based on antibodies formed by an individual lacking an antigen, can be different than expressed by the gene. Antigens can be a mosaic of determinants or epitopes influenced by other exons. The genotype represents the genetic makeup, that is, the true expression of the genes inherited by the individual.

Alloimmunization in chronically transfused individuals

The risk of alloimmunization is a major concern for those dependent on transfusion therapy. **Table 1**, "Rates of Alloimmunization in Transfused Receipients" is a summary of those alloimmunization risks in both the occasionally transfused and those with blood disorders dependent on transfusions. Erythrocyte alloimmunization occurrence ranges from 4.4 percent to 76 percent with a higher frequency of antibodies to antigens of the Rh system.[5] Age, gender (female), and number of transfusion (red blood cells) were major risk factors; however other risk factors were identified.

Rates of Alloimmunization in Transfused Recipients

Disease Condition	Alloimmunization Rate	Alloantibodies per Transfusion	Reference
General Population	4.4% to 10.5%	Not available	Summary of four studies as reported by Schonewille et al. Transfusion. 2016;56;311–320
Sickle Cell Disease	USA (22.33±0.13%) versus other countries (16.25±0.35%, p<0.000)	USA (0.45±0.003) versus other countries (0.20±0.005, p<0.0001)	Y. Zheng & R.W.Maitta Transfusion Medicine, 2016, 26, 225–230.
BThalassemia	Oman incidence 9.3%	Not available although anti-E (24%) and anti-K (24%)	Al-Riyami et al. Transfusion. 2018 doi:10.1111/trf.14508
Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia	15% with incidence rate of RBC alloimmunization was 1 per 10.5person-years	Not available	Sanz et al. Transfusion 2013;53:710-715.

Table 1.

Alloimmunization in blood disorders requires additional time in identification and delays treatment, all contributing to healthcare costs. Extended phenotypically matching blood has been used for many years but should be performed prior to transfusions and the formation of antibodies. For example, if an individual has been transfused, phenotyping may also detect a mixed field of transfused cells depending on if the transfused cells are still circulating in the recipient. This mixed red cell population would render the patient's own blood type indeterminable. For recently transfused patients, special procedures are required to separate the individual's own cells from those transfused. Blood group genotyping (BGG) does not have these limitations since the individual with a blood disorder can provide DNA anytime to determine the genotype of the red cell antigens.

Sickle cell disease (SCD) individuals are dependent on transfusions and many times demonstrate multiple antibodies to red cell antigens. Gehrie et al. point out that the greatest adverse events associated with transfusions to SCD individuals is the delayed hemolytic transfusion reactions, which can be life threatening.[6] Ten years ago the cost of treating an individual with SCD was about $460,000.[7] Since 2009, the U.S. national health spending has increased from $2,495.4 billion to $3,337.2 billion in 2016; a 25.2 percent increase. While current data is not available specifically for SCD, it can be assumed that SCD treatment and transfusion medicine workups have also increased by a comparable rate. Campbell et al. recommends hemoglobin S negative, prophylactically matched antigens for Rh and Kell in SCD patients.[8] Not surprisingly, extra attention to extended phenotypical matched antigens have also been effective in those general surgery patients by reducing their alloimmunization rate by 65 percent.[9]

Cost effectiveness of alloimmunization prevention

Prevention of alloimmunization in blood disorders such as SCD, thalassemia, and myelodysplasia syndrome is costly. Cost of serological testing and ordering specific blood is expensive with the 2019 CMS Outpatient Prospective Payment reimbursement set at $32.89 per Rh(d) phenotype and $271.73 for donor antigen typing. In addition, success with serologic matching of antigens, especially in African Americans is variable based on high frequency of variant Rh alleles in the SCD population. On the other hand, a genotypic matching program could offer cost savings since the recipient and donor are only genotyped once. Many blood centers have initiated genotyping and maintaining on a set number of reliable donors with genotype status in their available donor pool. For example, the French have developed a strategy for providing genotypically matched blood to "high-responders" (increase alloimmunization) and newly diagnosed SCD patients.[10] In the U.S., the National Institutes for Health (NIH), and the Wellcome Trust have funded the MedSeq Project. (The MedSeq Project, funded by the NIH, was the very first study exploring the use of whole genome sequencing (GS) in both a healthy population and a population with suspected genetic cardiac disease.) According to Lane et al., "By enabling more precise antigen-matching of patients with blood donors, antigen typing based on whole-genome sequencing provides a novel approach to improve transfusion outcomes with the potential to transform the practice of transfusion medicine."[11]

BGG has been strongly advocated to determine appropriate Rh immune globulin therapy (RhIg) to prevent the formation of alloimmunization to anti-D. RhIg is a biological product extremely effective in prevention of hemolytic disease of the fetus and newborn (HDFN) due to anti-D alloimmunization. The D antigen is mosaic of epitopes and if one part of the mosaic is missing the observed laboratory characteristic may be interpreted as "weak." In the U.S., there is a lack of standardization to workup and interpret a weak D. In many medical facilities, a woman serologically phenotyped as a weak D, and if she were of child bearing age, would be managed as a D negative and would receive RhIg therapy. A weak D is considered to be a non-reactive or less than a 2+ reaction, usually detected only by 37° C incubation and anti-D binding with anti-human

globulin. Sandler et al. advocates that BGG to confirm the D status would avoid at least 24,700 unnecessary ante- and postpartum RhIG injections.[12] In 2018, the mini-dose used for ante partum treatment was covered at $34.74 and $95.39 for the postpartum RhIG injection; genotyping would save from $858,078 to $2,356,133 in cost avoidance from RhIG injections. Furthermore, Rh negative blood is overused, especially in those with a serologic weak D phenotype. If the genotype were determined, approximately 48,000 units of RhD negative blood could be available for emergency cases when RhD negative blood is needed for mass transfusion protocols. Sandler et al. advocates the expansion of genomic testing to personalize medical care.

Multiple myeloma is a blood cancer of malignant plasma cells in the bone marrow. A monoclonal antibody (anti-CD38) also known as Darzalex (daratumumab) has recently been used for treatment of multiple myeloma in which other lines of therapy have been ineffective. Success with daratumumab has been the basis for expanded blood disorder trials.

Since the red cell membrane has CD38 receptors, daratumumab often results in a positive indirect antihuman globulin test result. Daratumumab (anti-CD38 mediated) positive indirect anti-human globulin test can persist for up to six months following the last treatment. Prior to daratumumab administration, the drug manufacturer recommends a blood type and antibody screen.[13] However, if blood is needed in the course of treatment, the blood bank is often challenged to determine if there is a new underlying antibody. Dithiothreitol (DTT) is limited and may not provide a clear understanding of any potential alloimmunization to antigens sensitive to enzyme treatment. Neutralizing substances to anti-CD38 is a potential tool in serological workups, but may not be available. But BGG can be the most beneficial, providing clarity of the patient's genotype without laborious and expensive techniques. BGG directed at the patient's DNA is not susceptible to interference by transfused products or infused drugs.

Changing the paradigm from phenotype to genotype determinants

In the last five years, the Food and Drug Administration (FDA) has approved two red cell genotyping assays based on detection of single nucleotide polymorphisms (SNPs) on selected genes. In 2014, the pre-market approval of the Immucor PreciseType HEA Molecular BeadChip Test was cleared. This device is indicated for the molecular determination of allelic variants that predict 36 erythrocyte antigen phenotypes.

In 2018 the FDA approved ID CORE XT, a molecular-based assay used in blood transfusion medicine to help determine blood compatibility. The ID CORE XT has its origin with the BloodGen project, funded by the European Commission (2003-2006) to investigate DNA array-based methodology for genotyping blood donors or patients. The FDA approved assay can be used to determine blood donor and patient non-ABO red blood cell (RBC) genotypes. The FDA identified the ID CORE XT as the only blood group genotype assay cleared to genotype the polymorphisms and predict the allele genotypes and antigen phenotypes of the blood group systems listed in **Table 2 (available online)**, as an alternative to serology. In December 2018, the FDA issued their final guidance on, "Labeling of Red Cell Units with Historical Typing Results."[14]

FDA cleared red cell molecular assay comparison

Table 2 provides a comparison of the two FDA approved HEA molecular assays. Package inserts and FDA's Summary of Safety and Effectiveness are available online at www.fda.gov. The key differences are:

- HEA BeadChip Kit (PreciseType) is an in vitro diagnostic test intended for the molecular determination of allelic variants that predict erythrocyte antigen phenotypes predictive phenotypes as final result. The ID CORE XT is FDA approved for reporting genotypes. Predictive phenotypes do not require additional serology for labeling or reporting.
- ID CORE XT predicts the Miltenberger (Mia, MNS7) antigen. Detection of the Miltenberger (Mia, MNS7) antigen is a discrete antigen of the MNS system. The Mia is the product of a hybrid gene, probably a mutation or crossover events of glycophorin A and glycophorin B responsible for the unique glycophorin hybrid peptide, Gp.Mur phenotype. In the Japanese and white population, the frequency is very low, 0.006 percent and 0.0098 percent, respectively. The frequency is much higher in other parts of Asia, such as Chinese (seven percent), Thai (10 percent) and even higher in indigenous tribes in Taiwan (21.2-88.4 percent). Antibodies to the Mur and the Mia antigen can cause hemolytic transfusion reactions (HTR) and HDFN.[15] PreciseType detects the Hemoglobin S mutation in the Beta Globin gene. Results from this mutation detection are not intended for diagnosis of SCD.
- PreciseType is predictive for Landsteiner and Weiner (LW) and Scianna antigens. However, antibodies to LW are not considered clinically significant and have not been implicated in HTR or HDFN. Antibodies to Scianna (anti-Sc1 and anti-Sc2) are not thought to be implicated in HTR or HDFN, but mild cases of HDFN have been reported. Antibodies to Scianna are detected by anti-human globulin technique and can be resistant to enzyme treatment.

The use of molecular testing has evolved transfusion medicine. This is especially true regarding transfusion support for blood disorders dependent on transfusion therapy. The ability to go beyond serology and predict the genotype has helped to resolve serologic issues and focus on the exons responsible for the antigen structure. As molecular testing continues to improve—and the reality of Next Generation Sequencing becomes affordable—it is possible in the future that matching transfusion recipients and selected genotypically matched donors will be standard practice.

Please visit mlo-online.com for references, table 2, and key points.

Jerry A. Holmberg, PhD, MS(CLS), MT(ASCP) SBB, serves as Senior Director of Strategic Scientific Innovation for **Grifols Diagnostic Solutions, Inc.** He has more than 35 years in all areas of laboratory medicine with a concentration on blood bank operations, education, quality, and policy.

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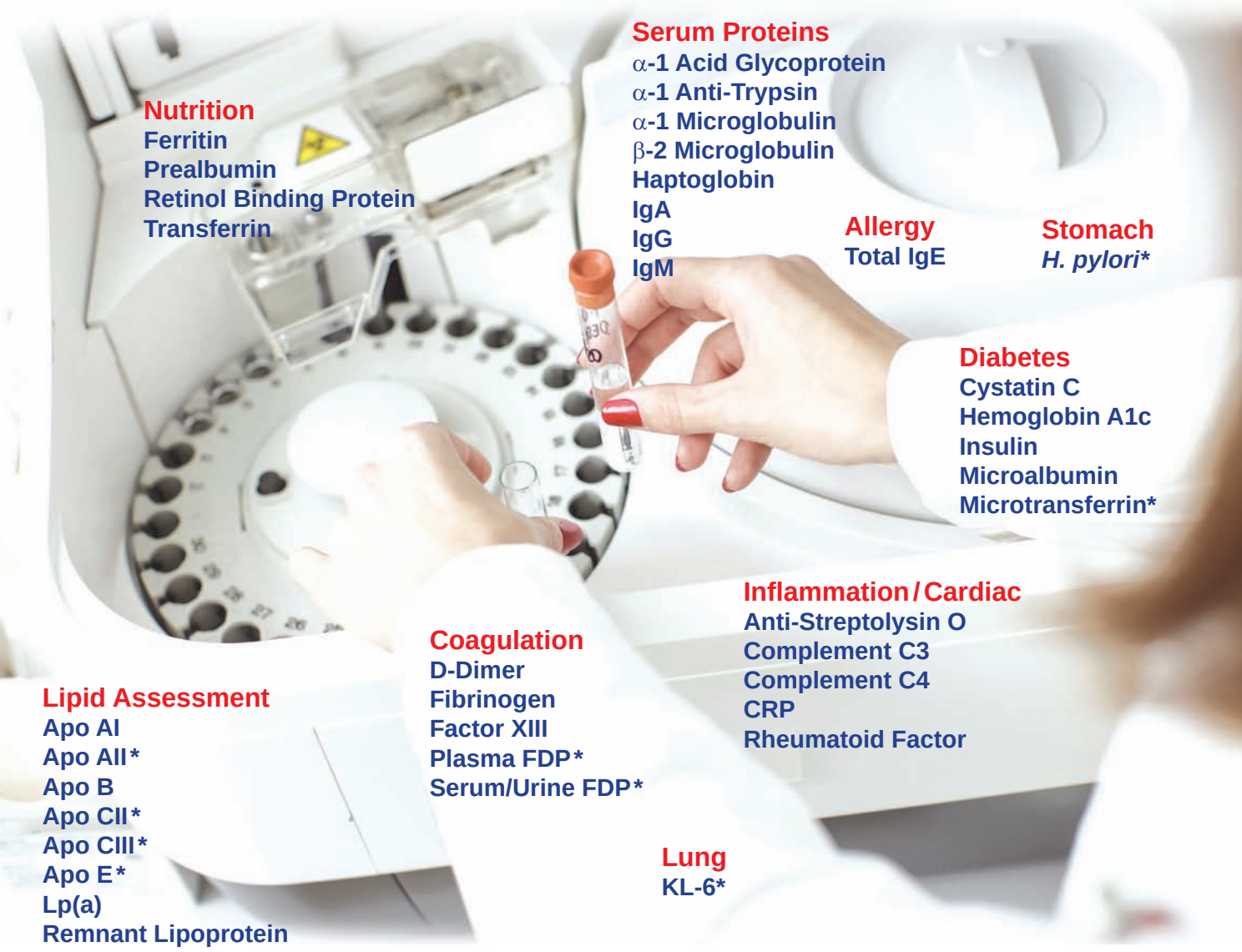

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It's all in the genes—expanding molecular testing to improve healthcare for those with blood disorders

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TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: ⊗

1. **Who was responsible for greatly improving the knowledge and understanding of DNA over 60 years ago?**
   - a. James P. Allison
   - b. Friedrich Miecher
   - c. Watson and Crick
   - d. Karl Landsteiner

2. **The part of the gene that codes for amino acids responsible for protein structure that is on the cell surface or in the plasma is called the**
   - a. exon.
   - b. intron.
   - c. promotor.
   - d. chromosome.

3. **Protein products on the cell surface or in the plasma can indicate normal or abnormal cellular function.**
   - a. True
   - b. False

4. **Who was the first scientist to demonstrate phenotypic differences of the ABO blood group system?**
   - a. Karl Landsteiner
   - b. Watson and Crick
   - c. Levine and Stetson
   - d. Gehrie

5. **Which precursor gene is the ABO system controlled by?**
   - a. A
   - b. B
   - c. O
   - d. H

6. **Some studies have demonstrated a relationship between the ABO blood group system and other carbohydrate blood group systems with**
   - a. certain infectious diseases.
   - b. malignancy.
   - c. cellular adhesion.
   - d. all of the above

7. **The blood group systems of clinical significance after the ABO system are**
   - a. Rh and Duffy.
   - b. Duffy and Kidd.
   - c. Rh and Kell.
   - d. Kell and Duffy.

8. **The phenotype is the true expression of the genes which were inherited by the individual and the genotype is the observed characteristics of the gene.**
   - a. True
   - b. False

9. **In the immunohematology lab, the patient's_____ is tested and reported in terms of antigen expression.**
   - a. genotype
   - b. phenotype
   - c. exon
   - d. intron

10. **What are the occurrence rates of alloimmunization in patients dependent on transfusion therapy?**
    - a. 5.3-85 percent
    - b. 10-25 percent
    - c. 40.0-78 percent
    - d. 4.4-76 percent

11. **What is/are the top risk factor(s) in the development of red cell alloimmunization?**
    - a. age
    - b. gender
    - c. number of transfusions
    - d. all of the above

12. **Blood group genotyping eliminates all of the limitations that exist with blood group phenotyping.**
    - a. True
    - b. False

13. **Which project tests for whole-genome blood group sequencing in blood disorder patients in order to improve transfusion testing and outcomes?**
    - a. MedSeq
    - b. SeqMed
    - c. GenomeTX
    - d. BloodGen

14. **Besides transfusion therapy, which other area of immunohematology is being studied for the use of patient genotyping?**
    - a. specimen collection containers
    - b. determination of RhIG therapy
    - c. transfusion reactions
    - d. none of the above

15. **When a patient is determined to be phenotypically weak D, the Rh status is managed as a D-positive individual.**
    - a. True
    - b. False

16. **According to Sandler et al., genotyping of a patient's D status will eliminate at least _____ ante- and postpartum RhIG injections and save at least _____ units of RhD negative blood.**
    - a. 10,300; 58,000
    - b. 14,700; 48,000
    - c. 24,700; 48,000
    - d. 39,200; 58,000

17. **Blood group genotyping can aid in the elimination of expensive and time-consuming laboratory techniques such as DTT and neutralizing substances to anti-CD38 in patients with**
    - a. thalassemia.
    - b. multiple myeloma.
    - c. sickle cell disease.
    - d. iron deficiency anemia.

18. **Which red cell genotyping assay predicts 36 red cell antigen phenotypes?**
    - a. ID CORE XT
    - b. Precise Type HEA Molecular Bead Chip
    - c. Precise Type Core XT
    - d. all of the above

19. **Which molecular test is used to determine red cell genotypes and predict the allele genotype and antigen phenotypes of many blood group systems?**
    - a. ID CORE XT
    - b. Precise Type HEA Molecular Bead Chip
    - c. Precise Type Core XT
    - d. all of the above

20. **What clinically significant antigen—which has high frequency in parts of Asia—is not found in the PreciseType test, but is determined in the ID CORE XT test?**
    - a. Jsa and Jsb
    - b. Doa and Dob
    - c. Dia and Dib
    - d. Mur and Mia

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TYPING

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Auto-verification rules—now what?

By Anne L. Tate, MT(ASCP),SC, MBA

So, your rules auto-verification program is up and running. Your auto-verification rate is 85 percent or better. Your lab productivity has dramatically improved and you are happy! It has been over a year since you verified your rules. You've made a few changes, inactivated and added some rules, edited your value lists and now your CAP inspection is coming up. Now what? Do you have a plan to make sure that your rules changes are effective? Will they have the desired outcome with the same or improved auto-verification rate?

The quality of the auto-verification rules when implemented has a direct impact on the efficiency of the rule logic and outcome of patient results. However, post-implementation and over time, it becomes a more challenging task to maintain consistent quality of those decision rules. Changes are made to rules for specific clinical reasons, but not always in the context of the full rules set. Inadvertent changes can creep into the rules software that can have unintended consequences on rule performance. Often rules oversight is not centralized; several staff could be involved in rules configuration, and, although well-intentioned, could introduce issues that go unnoticed.

A rule quality monitoring program can help laboratories establish better controls that continuously assess rule quality and performance. Rule performance monitoring should be incorporated into the laboratory's overall quality assurance program to ensure the decision rules are meeting a high auto-verification rate *all of the time*. Even the smallest of changes can impact the quality of your rules and erode your auto-verification rate with intended or often inadvertent changes to the rule base. A rule quality monitoring program has the benefit of being able to pinpoint problems and detect subtle changes to your rules operation to ensure no unintended modifications have been introduced into your rule sets.

The following are recommended components of an auto-verification quality assurance program that can assist in maintaining the integrity of your auto-verification rules set over the long-term. Rules sets are never static and require a multi-layered approach to keep a rule base intact and functional to support your patient quality and safety goals.

Rule quality assurance program recommendations

- **Auto-verification rate monitoring**: Periodic review of your auto-verification rate (AVR) is highly recommended to identify any rule degradation or opportunities for improvement. There is a direct relationship between rule integrity and performance. Each lab or site should establish an AVR that is achievable based on the lab's clinical objectives. An AVR is a key laboratory operational metric to ensure that when rules are added, adjusted, or changed based on clinical practices that the AVR is not impacted or reduced as a result of rule maintenance activities. Checking your AVR on a consistent basis will detect any latent or unexpected changes that could impact rule performance.

- **Verify rule values**: Periodic review of rule input values are important to confirm they are current with the lab's clinical practices. On an annual basis, a process must be in place to confirm that the data variables and value lists are current and accurate within the rule set. Rule inputs such as reference ranges, critical values, delta logic, and instrument flagging are important to verify to protect against any missing or inadvertent changes to the rule set that could degrade the AVR. Create a source of truth document to establish a baseline for on-going reference and for use in verifying your rules inputs.

- **Check rule build logic**: An important component of rule quality is the configuration of the rule according to the correct software syntax and the order of the rule actions. Because rule executions may occur in steps with rule parent-child relationships, the rule operation workflow must be reviewed periodically to identify any gaps and to avoid multiple failures in the rule processing workflow. An annual process of verification of mapping of the parent-child relationship is recommended before rule verification testing to ensure no changes have occurred that might interrupt the rule prioritization workflow.

- **Maintain rule traceability matrix**: Each laboratory should have a definitive list of its auto-verification rules. All rule changes should be documented and tested in a 'test' environment before placed into production using good rule testing practices. Rules that are no longer needed should be inactivated (never deleted) to maintain rule traceability over time. A traceability matrix of each rule by number or identifier should be maintained to certify that all rules can be accounted for and no inadvertent actions have removed or deleted a rule or its contents.

- **Establish a rule verification testing schedule**: Auto-verification rules should be verified at key points to ensure viability. Rules should be tested at least annually to meet regulatory requirements, when there are changes to the rule components and when new rules are introduced. Creating a rule testing schedule for the year ahead will keep you on track to ensure your rules are always operating at peak performance.

Anne L. Tate, MT(ASCP),SC, MBA serves as the Director of Product Marketing at **Software Testing Solutions, LLC**. She has more than 25 years of experience in healthcare and specializes in clinical decision support rules and informatics.

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POCT made easier with informatics

By Daniel Gundler

As the healthcare industry moves closer to the patient's side, point-of-care testing (POCT) is becoming more relevant. With faster and easier access to results, healthcare providers can reduce lengths of stay and increase patient satisfaction by avoiding extended wait times for central lab results.[1]

With this positive trend come new challenges: How do point-of-care (POC) coordinators keep hundreds of devices up and running while managing training and certification and enabling secure access for thousands of operators? How do healthcare systems enforce quality control so that compliance and accreditation requirements are satisfied?

A POC coordinator's daily challenges

POC coordinators face many challenges associated with their responsibilities. These include making sure all POCT devices are up and running, keeping downtime rates low, and ensuring instruments are used correctly by staff members.[2] POCT devices often are dispersed in many locations across the hospital network and constantly change hands among staff members, increasing the likelihood that the instruments could be used by staff who are not properly trained on the devices. Consequently, POCT coordinators can easily lose oversight and control of POCT operations, which can cost time and money and affect the quality of results and even patient care.

Connectivity is a step often unintentionally missed during POCT implementation. With many market offerings, it is not uncommon for POC instruments to be purchased from a variety of vendors by different departments to meet the healthcare facility's specific testing demands or budget. Each POC device has its own specific user interface. This means coordinators must maintain—and be trained to use—several different software solutions. They must understand each instrument's functionality and limitations in addition to managing its quality control (QC), usage, and inventory. POC coordinators also must perform software updates for each analyzer to ensure security vulnerabilities are addressed. With all these tasks to manage, it is understandable why QC, adequate staff training, and oversight are key concerns for coordinators.

Maintaining POC instruments and overseeing the operators performing POC tests would be much easier if all the information and data from each instrument were accessible through one user interface in which coordinators could manage both the instruments and operators. POC informatics solutions enable POC coordinators to manage dozens of sites, hundreds of devices, and thousands of operators. Informatics is the process of taking data and turning it into useful information. With increasingly sophisticated capabilities and simpler interfaces, integrated and open POCT environments help to create a streamlined workflow for more-efficient program management.

Connecting all devices, regardless of the manufacturer

To arm POC coordinators with the information necessary for their management and reporting needs, manufacturers are offering tools that give them control over the factors most applicable to their level of oversight. With many different POCT devices commonly implemented in a single healthcare facility, an open middleware solution can help to improve workflow. One such solution can connect more than 180 models of POCT devices from 40 manufacturers to a central laboratory or hospital information system. This open connectivity gives POCT coordinators improved oversight of operations and instruments for their entire POCT program without forcing unnecessary conversion to a specific vendor's instruments, which may not be the right fit for a specific patient population.[3]

An open system receives data such as patient and QC results from POCT devices, technically validates the data, and forwards the test results directly into the electronic patient record. During this process, the system documents all POCT device data, offers remote monitoring of POCT devices, and provides quality and user management to ensure compliance with all quality assurance and regulatory guidelines.

Integrating one of the world's largest POCT networks with POC informatics

While POC informatics programs have been slower to take hold in the U.S., other countries have successfully implemented such programs, from which U.S. facilities can learn best practices. For example, Queensland Health operates and administers the public-health system for the state of Queensland in Australia. The health system faced the challenge of connecting and managing 300 POCT blood gas analyzers operated by over 8,500 users at more than 250 Queensland Health sites spread across Australia's vast east coast and inland region. The POCT analyzers run approximately 4,500 tests per day, producing large volumes of patient and QC test-result data that must be validated and transmitted to the lab information system at Queensland Health's headquarters in Brisbane.

A major challenge was the relative lack of resources and support in areas further inland from Queensland's east coast. In a region where the nearest pathology lab is 310 miles away and roads can be impassable for months, the ability to reliably produce quality-assured test results locally is critical in improving patient outcomes. Patients living on the coast have access to big hospitals, modern equipment, and support for pathology and radiology. The further you travel inland, the thinner the support becomes.

Achieving acceptable test-result quality was difficult in the more remote areas. This was largely due to the mobile, transient nature of the operator workforce, many of whom were hired through staffing agencies and moved frequently from job to job. POC coordinator, Cameron Martin, shared that it was difficult to keep staff trained and to track their training, and testing quality suffered as a result.

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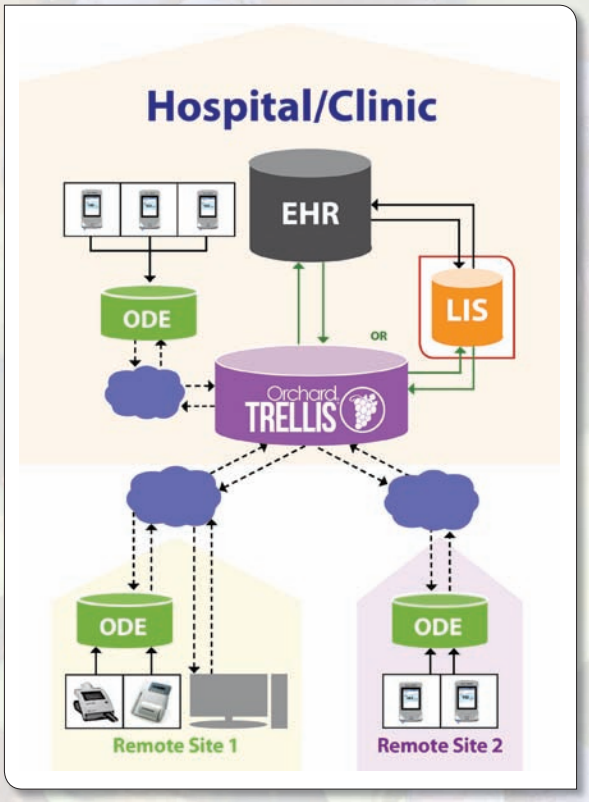

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After years of seeing error rates rise, Queensland Health was able to install an online training program. After much consideration, Queensland Health chose the open-connectivity POCcelerator Data Management System to consolidate its middleware. By adding the POCcelerator system, Martin can now train operators remotely, manage operator access, and precisely track their training so he knows which operators are current and which are not.

Installing the POCcelerator system has improved both the operations of the Queensland Health system and access to care across the country. By creating a well-connected POCT environment, instruments in the remote areas are used more frequently, and the results are recorded more accurately. Martin reported, "By making the system perform better, we can help deliver…a more reliable service in those areas."

At the POC, achieving high-quality results relies on operators making fewer errors. With better tracking capabilities for operator training, the POCcelerator platform has created better-trained operators who produce higher-quality results.

Conclusion

As the digitalization of the healthcare industry progresses, connectivity of testing devices is increasingly important and should not be overlooked. Fast and easy data access from everywhere within a healthcare network can lead to faster decision making, better patient care, and even reduced length of stay.

For POC coordinators, managing dozens of sites, hundreds of operators, and thousands of devices is a job unto itself. They can meet this challenge now and in the future with an integrated and open POCT environment that improves outcomes and workflow while enhancing care delivery across clinical pathways.

The outcomes achieved by the Siemens Healthineers customers described herein were achieved in each customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that others will achieve the same results.

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1 The expanded use of venous whole blood, arterial whole blood, and neonate arterial and heel stick whole blood samples throughout all hospital and all professional healthcare settings including patients receiving intensive medical intervention/therapy is pending 510(k) clearance with the FDA and is not available in the US.

*Roche data on file 2018.

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Capillary sampling for HbA1c testing

Tips to help reduce preanalytical errors

By Tania Mackenzie

It is estimated that nearly one in every 10 Americans is living with diabetes, with 1.5 million adults being newly diagnosed every year. Diabetes impacts over 30 million Americans and remains the 7th leading cause of death in the United States. Properly controlled diabetes can reduce mortality rates, yet nearly one third of Americans who have this condition remain undiagnosed.[1] This means the reliable detection of diabetes through HbA1c testing can have life or death consequences for millions of Americans annually.

Because HbA1c tests can be performed easily without fasting or having to drink anything, this test is often the first indicator that diabetes is present for patients. For those already diagnosed, the test provides insight into how well the patient is adhering to their treatment plan, or how well the treatment plan itself is working. Although a diabetes diagnosis is decided by HbA1c levels of 6.5 percent or higher, this test is also an effective means for determining prediabetes in patients with ranges between 5.7 percent to 6.4 percent. In prediabetic patients, studies have shown that moderate exercise and losing 7 percent of one's body weight can reduce a patient's risk of type 2 diabetes by 58 percent.[2]

Impact of preanalytical errors

It has become standard practice to perform the HbA1c test using a point-of-care (POC) system with a capillary blood sample. Compared to venous blood draws, capillary blood sampling has the advantage of being easier and faster to perform. Yet, despite its simplicity, obtaining a quality capillary blood sample can pose challenges—and if done improperly, can contribute to preanalytical errors. With a pervasive and destructive disease such as diabetes, diagnostic errors can have dire consequences. Even failing to detect prediabetes does patients a disservice, because it deprives them of a chance to correct behaviors that could prevent a chronic, life-altering condition.

Fortunately, many capillary testing challenges are easily overcome by following best practices and industry guidelines. By ensuring tools and sampling are performed appropriately, higher success rates can be achieved.

Five tips for reducing preanalytical errors

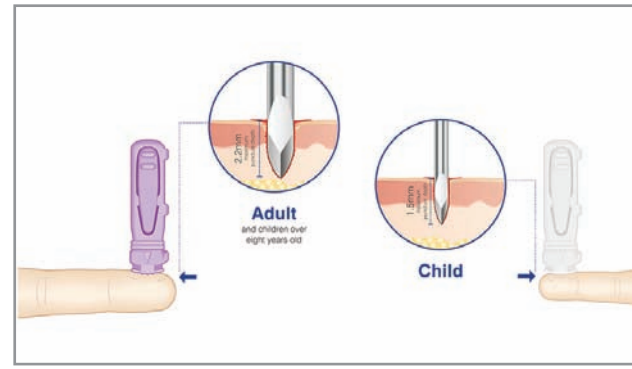
1. Know your blood volume requirements

The volume of blood required to perform a diagnostic test varies depending on the POC device being used and the specific test being conducted. As newer technology has emerged, blood volume requirements have been greatly reduced. Different POC devices perform optimally with specific sample sizes and too little or too much blood can impact readings. Familiarizing yourself with the blood volume requirements for your POC device is an essential first step.

Blood volume requirements vary by the type of test being performed and the number of tests being performed. When run alone, HbA1c tests require very low blood volumes (1-5ul)[3] that are typically achieved with thin lancets at shallow puncture depth (i.e., 30G x 1.5mm or 28G x 1.8mm). If performing multiple tests or testing on an individual with thicker skin, it may be necessary to use a larger lancet and puncture deeper.

2. Choose the right lancet

Safety lancets are available in a range of sizes and activation methods and determining which lancet to use will depend upon the patient, the diagnostic test for which the sample is required, and consideration of pain reduction. The latter factor is especially important for patients from whom samples must be collected repeatedly.



Selecting lancet length

The World Health Organization (WHO) reports that pain increases with lancet penetration depth,[4,5] which is partly determined by the length of the lancet being used. It notes that, when finger sampling in adult populations, the depth of penetration should not go beyond 2.2mm and that pressure applied during sampling compresses the skin so that ultimate puncture depth will be slightly greater than the length of lancet used.

In the U.S., many hospitals and labs carry specific lancet brands as per contractual arrangements, and often have several size variants available within the line(s) they carry. Safety lancet specifications vary by depth of penetration and gauge size. The depth of penetration is pre-set and straightforward, with some safety lancets going as deep as 3.0mm and others as shallow as 0.5mm. Assuming other variables are constant, the deeper the lancet penetrates, the greater the blood volume it will produce. Gauge size

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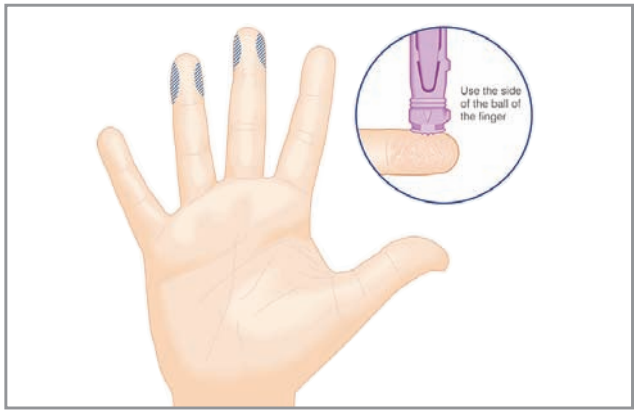
dictates the diameter of a lancet. Unlike depth of penetration, the higher the gauge size, the smaller the lancet diameter. For example, a 30-gauge lancet is thinner than an 18-gauge, and if all other variables are constant, should result in a smaller blood sample. Beyond device specifications, bevel geometry and activation method may also impact blood volume, and these will vary by manufacturer.

3. Selecting a suitable sample site

For adults and children over 6 months (weighing more than 22lbs), WHO recommends testing be done of the side of the ball of the finger and should be restricted to the middle and ring fingers. The thumb and index fingers are precluded because of the potential for calluses, and the little finger because the tissue is thin and there is a higher risk of hitting bone.[4]



Finger puncture site selection

There are a number of factors which influence the possible blood volume derived from any given sampling episode. These include patient hand temperature, lancet specification, and post-lancing massage technique. Research has highlighted the wide variation of blood volume achieved from site to site in the same patient and with the use of different post-lancing techniques, such as pressure application.[6] When conducting a POC test, it is recommended that the safety lancet needle gauge (thickness) and length be chosen to collect the minimum volume of blood required to successfully complete the diagnostic test.

4. Perfecting your technique

Technique is important for reducing sample contaminants and for achieving adequate blood flow.

Prior to lancing, the sample site should be cleaned with alcohol and allowed to dry.[4] If a large blood volume is required, the sample site can be warmed prior to cleaning. Ideally, the site should then be lanced in one quick motion, and the first drop of blood wiped away to avoid contaminating the sample with tissue fluid or debris. Gentle pressure should then be applied to encourage the flow of blood into the collection device, while avoiding pressing too vigorously, as this may dilute the sample with plasma and increase the probability of hemolysis.[4]

5. The patient's experience

Research into the pain associated with the use of safety lancets highlights that the key factors implicated are ease of skin penetration and the size of the resultant injury.[5] The first of these factors is determined by lancet geometry and the quality of the lancet tip. The second factor is determined by lancet diameter and penetration depth. In order to make the procedure as comfortable as possible for the patient, a good quality lancet should always be selected, with a lancet size that provides just enough blood for the procedure. Some safety lancets go further to help reduce pain, with design features that reduce pressure or help distract the nerve endings.

Conclusion

POC testing offers a fast and reliable means for conducting HbA1c testing, however it may be subject to preanalytical errors if capillary sampling is not performed appropriately. By understanding blood volume requirements, selecting the right tools, and following best practices it may be possible to reduce preanalytical errors for improved testing accuracy. With HbA1c representing a key means of identifying diabetes and prediabetes, as well as treatment efficacy over time, accurate results are imperative to helping improve outcomes for millions of patients living with diabetes across the U.S.

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"Trusted Care" leads to zero harm at Travis AFB Clinical and Pathology Lab

By Merrie Schilter-Lowe

There are numerous places in a hospital where things could go wrong. As a result, the Clinical Laboratory and Anatomic Pathology Flight at the David Grant USAF Medical Center (DGMC), located at Travis Air Force Base in California employs "Trusted Care" principles to combat errors and reinforce a zero-harm patient care environment.

DGMC operates the Air Force's largest clinical laboratory, supporting 465 health care providers and more than 325,000 patients per year. The staff of 91 medical laboratory scientists, technicians, phlebotomists, and five board certified pathologists perform 1.2 million tests annually.

But what really distinguishes the lab from its civilian counterparts is that 85 percent of the staff are active-duty enlisted members with an average of three years of lab experience. Civilian technicians have around 14 years of experience.

Unlike civilian labs, the DGMC lab also must contend with constant personnel turnovers, deployments, and a staff called on to perform additional duties and complete military training requirements. Despite this, the DGMC lab continues to deliver high-reliability test results and blood products by embracing the principles of Trusted Care.

In 2014, the Military Health System and its civilian partners embarked on a mission to evaluate its healthcare system to ensure the best care was being delivered to patients. After researching and studying the leading practices in the civilian sector, the Air Force Medical Service adopted the Trusted Care principles. The DGMC was a pilot location.

"The Air Force hired a civilian company to walk us through from adoption to implementation of high reliability principles," said Elizabeth Nelson, DGMC patient safety manager. "We've been on the Trusted Care journey a little over three years now and we're getting closer to that goal of zero harm."

Domains of change

The four domains of change are: (1) leadership engagement; (2) culture of safety; (3) continuous process improvement; and (4) patient centeredness. Each domain builds upon each other to achieve high reliability and the goal of zero harm.

"What we want Trusted Care to mean to our patients is that we are constantly working toward zero harm, so they can completely and absolutely trust us—literally with their lives and the lives of their loved-ones," said Lt. Col. Heidi Clark, Nutritional Medicine Flight Commander and patient safety coach to organizations like the laboratory, which is assigned to the 60th Diagnostics and Therapeutics Squadron.

DGMC has more than 70 safety coaches—staff members trained to help reinforce specific behaviors that have been proven to develop safe medical care.

"Behaviors like exercising a questioning attitude or concern in an incremental way such as: 'I have a concern about this situation,' or 'I am uncomfortable with this… we need to stop until my concern is addressed," explained Clark.

Staff Sgt. Kristopher Walton exercised a questioning attitude that, several years ago, could have earned him a reprimand. Walton was on weekend-duty when a physician requested a test that the lab's hematology equipment wasn't calibrated to perform. He explained this to the doctor, but she insisted he run the tests based on previous research.

"I didn't want to provide inaccurate results, so I called the on-call pathologist," said Walton.

The pathologist called the doctor to discuss the issue and finally gave Walton the green light to perform the test. Instead of a reprimand, Walton was selected the DGMC "Hero of the Week."

Supporting fundamental change in culture and behavior

"I think what's different now is that we are patient-centered and operating in a 'Just Culture,'" said Lt. Col. Patrick Kennedy, Clinical Lab and Pathology Flight Commander. A just culture encourages staff to speak up when they see situations and issues that could negatively impact a patient. This is incredibly important in the lab where four out of five patient diagnoses are made.

"Labs today help control healthcare costs. If we make the wrong diagnosis and the patient goes to surgery, that would cost the patient about $30,000 plus the pain and suffering," said Col. (Dr.) Al M. Elsayed von Bayreuth, associate chief of professional staff, staff pathologist, and the primary medical review officer.

"When a patient comes to the emergency department with chest pain, we don't know what the cause is, but the doctor can draw blood to test the level of troponin and we will know in less than 15 minutes if it's heartburn or a heart attack."

Treatment is "personalized" to the patient, Elsayed von Bayreuth said.

Quality assurance team

Even though the lab is vested in Trusted Care principles, the staff couldn't do the job as well without the quality assurance (QA) team. The QA team are lab technologists with at least a bachelor's degree and 10 or more years' experience in all areas of the lab.

"We have numerous indicators to make sure that the test results and blood products we send to providers are highly reliable, so they can take care of our patients," said Maria Langeslay, QA manager.

The Travis AFB lab is accredited by both the College of American Pathologist and AABB.

Nelson said it generally takes 10 years to see some of the changes she is seeing throughout the medical center. When

she arrived at Travis AFB in 2014, she said it was hard to discuss things that went wrong.

"We had to shift the focus from a 'who's fault is it'—blame and shame—to a just accountability that focuses on the process," she said. "The daily safety huddles are one of the tools used to change the culture."

The optimal time in the lab for the huddle is at shift change.

"Every day at 8 a.m., we hold a safety huddle to discuss patient safety issues from the previous night and what might crop up during the day," said Master Sgt. Kristin Barber, QA section chief.

"We want to know things like: Are we low on supplies? Are we only 80 percent manned today? Do we have enough people covering the lab during lunch?"

The QA team and lab leadership ensure that technicians, pathologists, and even the administrative staff remain competent. They assess this by direct observations, blind tests, reviewing test results, and asking numerous questions.

"One of my jobs is to go onto the floor and talk to my techs; ask if they have any problems, give them a scenario and see how they solve it," said Kennedy.

Training is one of the key elements to having a competent staff, but training is a challenge considering that the military staff move to a new assignment about every three years.

"We are constantly trying to improve training," said Barber. "Each section has a civilian supervisor who has worked in this field for a long time. We rely on them for training and continuity, so no harm comes to a patient or staff."

Trusted Care principles permeate everything in the lab from providing reliable test results to improving customer service.

When the QA team realized in March (2018) that patients were waiting an average of 45 minutes for a blood draw, they conducted an Evidence-Based Project identifying the lab's peak hours.

"We had talked about the problem being manning, but it turns out that we only had one window open from 7 a.m. to 1 p.m.," said Langeslay. "Also, too many people were taking breaks at the same time, others were doing administrative work, or training students and personal care nurses."

By opening that second check-in window during peak hours and shifting training and paperwork to the afternoon, the lab reduced patient wait time from 45 minutes to 17.5 minutes.

"And we want to get it down to 15 minutes or less," said Langeslay.

Blood waste management

Quality assurance also identified a problem that was costing the Air Force money.

"When I started to work here in 2013, we were wasting 64 units of blood per month," said Langeslay. "I came from the private sector and the Veterans Administration where we saved as much as possible, so when they gave me that first report, I almost passed out."

The lab has dropped blood waste from 64 units per month to zero units. The difference is due in part to better inventory management.

"One of the problems was that our supplier was sending blood products that were close to the expiration date and we were accepting it," said Kennedy who arrived at Travis AFB in 2016.

"We looked not only at how the lab was using blood, but also how our counterparts on the wards were using it. We provided them a window of time when unused blood has to be returned to transfusion services before it becomes waste."

The lab also contracted with a different supplier who only charges for the blood used if the lab sends back the unused product in a timely manner.

"Quality assurance and Trusted Care go hand-in-hand," said Langeslay. "For me, QA is everything. We need that constant monitoring to deliver the best tests results."

Managing metrics

Speaking of test results, metrics are another high priority in the lab.

"Critical results need to be reported in 15 minutes or less," said Barber. "Stats need to be completed in less than an hour. We want to reduce that time even more."

A big-screen, wall-mounted TV allows techs to track stats and critical requests. The lab also uses a whiteboard, which is the first thing technicians see when they enter the lab, so staff can document concerns, and issues that need to be elevated to senior staff.

Perhaps the biggest culture change throughout DGMC is that leadership constantly encourages staff to submit patient safety reports, or PSRs.

"PSRs are enlightening; they help us track trends to see if we're getting better or worse," said Kennedy. "PSRs impact all areas in the medical center. If something happens in surgery, we want to learn from it, so it doesn't happen in dermatology or another department."

The definition of a high-reliability organization is an organization that has succeeded in avoiding catastrophes in an environment where normal accidents can be expected due to the risk factors and complexity.

If something does go wrong in the lab, the team uses an algorithm to determine the root cause and what to do about it.

"We ask if it was deliberate or an accident? If an accident, how can we prevent it from happening again?" said Barber. "Is it a lack of training or is it the process?"

Every staff member at DGMC is committed to providing the safest care to patients, said Clark.

"The only appropriate goal is zero harm, knowing that we may never reach it," she said. "Any less of a goal is unworthy for the trust that we are given as medical professionals. Any lesser goal encourages people to be satisfied with less than perfection; we have to keep striving to improve."

The lab staff understands that. In 2017 the Travis AFB lab was *MLO*'s Lab of the Year!

Merrie Schilter-Lowe, M.Ed, is a graduate of the University of West Florida. As a public affairs specialist at Travis AFB, CA she covers environmental issues for the 60th Air Mobility Wing and writes medical articles for the David Grant USAF Medical Center. DGMC is the Air Force Medical Service's flagship medical treatment facility in the U.S., providing a full spectrum of health care and patient-centered treatment to more than 500,00 Department of Defense and Department of Veterans Affairs beneficiaries in Northern California.

PCR for antibiotic resistance markers—not the whole story

By John Brunstein, PhD

In this month's episode, we're going to revisit a topic which this space has touched on before—not because things have changed much in the space (they haven't), but because these types of tests are becoming even more commonplace. It's worth reiterating for the end users of these test types what the associated test approach strengths and weaknesses are, and what caveats to interpretation should be borne in mind when reviewing results.

The tests we're discussing are any molecular (DNA or RNA sequence based) method which purports to tell whether a specimen associated microbial organism will be susceptible or resistant to a given antibiotic (or usually, a family of structurally and functionally related antibiotics). Usually these approaches are PCR based but as followers of this column will know, there's more than one way to amplify and/or detect a nucleotide sequence and our considerations here will apply to all of these.

Genotype doesn't equal phenotype

Let's start by reminding ourselves what a molecular assay detects (the presence, and perhaps the abundance of, a specific predetermined DNA or RNA sequence; in other words, a *genotypic trait*) and what defines antibiotic resistance in a microorganism (the ability of the microorganism to grow, more or less unhindered, when exposed to a set concentration of the antibiotic agent; that would be a *phenotypic trait*). The primary issue in a nutshell is that genotype does not equal phenotype; it equals the potential for a phenotype. What's clinically relevant is the phenotype, so why do we test for genotype at all?

The answer of course is that phenotypic testing is slow compared to the possible pace of clinical outcomes. Actually isolating the organism(s) from a sample and getting MIC (Minimum Inhibitory Concentration) real phenotypic values to compare against CLSI breakpoints can take days, which the patient may not have. Presumptive application of antibiotics, particularly ones with wide spectrums of action, is rightfully frowned upon as it promotes increased frequency of antibiotic resistance. Molecular tests step into this challenge because they can be done in hours and have a high degree of *correlation* to phenotypic antibiotic resistance behaviour. Bottom line, and ***take home message number one for today: they're fast, and very often correct, and so they provide a rational basis to support immediate therapeutic choices.*** That's great but it's a mistake to not recognize that this is still—by means of being a correlate measure and not a direct measure—an aid to empiric therapy.

If molecular test results are just a correlate to the phenotypic traits we actually care about, what are the ways that this correlation—or our assumptions which form the basis for this correlation—can fall down? Some of the mechanisms by which this happens include:

- **Phenotypes can arise from unrelated mechanisms.** For example, one major family of antibiotics is based on what's known as a "beta-lactam ring" molecule, and includes penicillins and cephalosporins. Some microorganisms develop enzymes (beta lactamases) which are able to break these down before they can act to interfere with cell wall growth; phenotypic resistance to beta-lactams is thus strongly suggested by detection of certain beta-lactamases in an organism. Just because an organism doesn't have beta-lactamases though doesn't necessarily mean it's susceptible to beta-lactams. Other completely different mechanisms such as efflux pumps can lead to exactly the same phenotype.[1] ***Take home message number two: we don't always test for, or necessarily even know, all of the mechanisms by which an antibiotic resistance phenotype can occur.***
- **Genotypic data may be incomplete.** Let's stick with our above example of testing for beta-lactamases. A first issue is that there are a lot of different versions of these genes, with differing sequences—and recall that a strength of molecular testing is its excellent specificity, which can be down to differentiating single nucleotide variations. That's not so much a strength here as a limitation; a mutation under a priming site can reduce or even abolish amplification and thus detection of the gene. It's also good to bear in mind that most molecular methods like PCR look at small portions of a gene, not the whole gene. Mutations elsewhere in the gene will not effect detection but might change activity of the protein product, leading for instance to a false impression of antibiotic resistance in a case where the gene is detected but has low activity (i.e. it would fall below MIC breakpoint in phenotype). In fact, mutations not even in the gene but in promotor regions might play a role, either increasing or decreasing phenotypic expression (tests based on expressed RNA levels would be one way to counter this effect, but the relative difficulties in handling RNA as opposed to DNA generally outweigh this benefit).

Of course, the companies producing validated assays in this application space have approaches to mitigate this issue, including selecting target gene regions with the lowest diversity (or biologically, the highest selective pressure against mutation), use of multiple primer sets to cover gene families, and even ongoing surveillance-by-sequencing of pathogenic organisms to detect novel resistance gene variants. In theory it's possible to design and deploy additional or modified primer sets to cover novel target gene variants, but in practice this is a very slow process to clear regulatory approval; you need to know details of analytical and clinical performance (sensitivity, specificity, PPV, NPV) of the 'modified' assay before use, and the cost and time to assess, submit for approval, and release such 'assay updates' is generally prohibitive. ***Take home message number three: most molecular tests examine a fraction of target gene(s) as a surrogate for the whole, which may be misleading. Take home message number four: microorganisms trust in crowdsourced solutions to selective pressures, and can develop and deploy selected variations rapidly and without bureaucracy or rules.*** That's a challenge to keep up with, and molecular tests only look for what we know to look for.

• **Mixed cultures can be very misleading.** We discussed above how molecular methods' specificity is not always a benefit in this space; that also turns out to be true of its intrinsic sensitivity. If a clinical sample contains more than one organism—perhaps trace quantities of something else, which doesn't necessarily even need to be viable—then molecular methods can come back with multiple organisms detected and multiple antibiotic resistance markers, but without ways to determine associations. In other words, which organism has which resistance markers? This can be handled to some extent by use of quantitative methods as opposed to purely qualitative detection, and then pairing up organism "identity signal strengths" with "antibiotic resistance marker strengths" to see which sets match. (In reality it's not quite that simple, as issues like relative copy numbers of the antibiotic resistance gene(s) and the organism marker(s) come into play, their relative amplification efficiencies, and the like; also, one might get cases with signals of similar amplitude for all organisms and markers. In at least some cases though this approach can help correlate resistance markers to specific organisms detected. Another tool in unravelling the multi organism/multi resistance marker scenario can be empiric data, in as much as some organisms haven't been previously observed to carry certain types of resistance markers, or do so in only rare cases; if you're lucky, you may be able to assign a mix of organisms and resistances out of a mixture by this with an acceptably high degree of probability. Finally, there are for some organisms and some markers particular molecular assays which can unequivocally pair a resistance marker to its host organism—most readily done in examples where the resistance marker, if present, will reside at a known, genetically conserved organism genome locus and the test can be designed to flank both organism and resistance marker genetic components. ***Take home message number five: beware of specimens positive for multiple possible pathogens and multiple antibiotic resistance markers. Some assumptions are probably being made to decipher that mixture.***

What does all of this mean for application of molecular testing in antibiotic susceptibility? It means that it remains a powerful, fast tool for helping to direct empiric therapy choices, and its application is greatly preferable to blind empiric therapy (that is, based purely on statistical past phenotypic susceptibility traits for a given organism). It also means however that it's far from being a fire-and-forget solution to antimicrobial therapy choices. Emerging methods like mass spectrometry may prove to be even more useful here. Recall that this isn't a "molecular method" by traditional definition of analyzing DNA or RNA – rather it has the ability to directly query a sample for the presence of characteristic fragments of key enzymes or intermediary metabolites which can relate to a particular antibiotic resistance mechanism. This then is one step closer to examination of final phenotype than is molecular testing, although its interpretation too may involve some of the same assumptions (and potential for being mislead) described above.

Clinical assessment of response remains key

While molecular susceptibility testing is a fantastic tool, it's important for end users of these technologies not to be lulled into a false sense of complacency that they are somehow infallible. Clinical assessment of patient response and (where possible) actual traditional bench microbiology—manual or automated—in determining real phenotypic resistance is still the essential final step in evaluating whether the myriad assumptions inherent in taking a genotypic result and extrapolating to a phenotype hold true in each and every case. In the end of the day, what matters to the patient is the end result. In cases where clinical response isn't what was expected, it's good to bear in mind all of the chain of assumptions which underlay conversion of molecular data to therapy choices. While the examples covered here aren't an exhaustive list of what those are, they're at least some of the more likely points for discrepancy to occur.

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Longitudinal performance of mRNA-based HPV testing as compared to DNA-based testing

By Thomas Iftner, PhD

Cervical cancer mortality has declined substantially since the 1971 introduction of cervical cancer screening by cytology (Pap smear). Moreover, the recognition that long-term (persistent) infection with any one of 13 high-risk human papillomaviruses (HPVs) may cause precancerous and malignant cervical lesions has led to the introduction of HPV testing as a co-test to cytology.[4] HPV testing offers improved sensitivity and results in earlier detection of abnormalities that are likely to progress to cancer compared to cytology alone.[3,7,8] A lower risk of cancer or high-grade neoplasia being detected at a second screening has prompted suggestions that the interval between screenings can be safely extended beyond three years.[7] This is beneficial because more than 80 percent of HPV infections clear spontaneously within two to three years of detection, making it advantageous to maintain screening intervals of at least three years in order to avoid mistaking transient for persistent infections and overtreating the women tested.

DNA-based HPV testing: sensitive but not sufficiently specific

There are numerous HPV tests available, and combined Pap and HPV testing (co-testing) is now widely accepted as the best means of realizing additional reductions in cervical cancer through the recognition and prompt (early) treatment of high-risk HPV-positive lesions before they progress to cancer.[1,9] Combined testing does not increase the burden for patients, as the two tests can be performed using a single swab. However, questions remain about the preferred method for HPV testing in screening protocols.

At present, there are nearly 200 tests for HPV, which include a number of nucleic-acid based tests. Among these, DNA-based tests have proven higher sensitivity; however, in patients with positive results, it is important to differentiate between transient and persistent infections in order to determine whether follow-up is required. With a DNA-based test, like the HC2 HR HPV test (Qiagen), detection of viral DNA not linked to an active cell infection and cross-hybridization with numerous HPV types not linked to cervical cancer risk means that positive results of DNA tests can lead to overdiagnosis of precancerous abnormalities,[8] prompting unnecessary follow-up testing (colposcopy), and treatment.[2] Moreover, HPV DNA tests are also likely to provide false-negative results because integration of the viral genome with the host genome over time typically decreases HPV DNA levels as infections progress toward cancer.[10] In contrast, RNA levels increase during viral integration because the expression of viral oncogenes escapes viral control.

mRNA-based HPV testing: a needed refinement

A single mRNA-based test, the Hologic Aptima HPV test, has been approved by the FDA in the United States. This test was compared with the test considered to be the current benchmark among the DNA-based assays used for HPV screening, the Qiagen Hybrid Capture 2 test.[5,6] In a 2015 study,[5] mRNA-based and DNA-based testing in a population of 10,040 women (aged 30 to 60 years) showed statistically similar sensitivities for detecting CIN2+ or CIN3+ lesions. However, the specificity (<CIN2) and positive predictive value (≥CIN2+) of the mRNA-based test were significantly improved compared to the DNA-based test.

In addition to these results, leading experts considered it necessary to obtain long-term data demonstrating the longitudinal negative predictive value of the mRNA test. This data was essential to confirm that the increased interval between screenings proposed for DNA-based testing would also be appropriate for mRNA-based screening. In a 2018 follow-up to the above-cited study, 3,295 triple test-negative women underwent repeat screening a median of six years after their original test.[6]

In addition, 411 who were test-positive at baseline but were not diagnosed with or treated for precancerous lesions (CIN3) were followed up annually for up to a total of five years (as long as they were test-positive on HPV and/or cytology).

Table: Six-year cumulative incidence, risk per 1000 women screened, and negative predictive value among women who tested negative at baseline

	Cumulative incidence, % (95% CI)	Risk per 1,000 women screened, n (95% CI)	Negative predictive value*, % (95% CI)
CIN2 or worse			
RNA-negative	0.62 (0.24-1.59)	6.2 (2.4-15.9)	99.38 (98.4-99.8)
DNA-negative	0.47 (0.27-0.81)	4.7 (2.7-8.1)	99.53 (99.2-99.7)
LBC negative	1.66 (0.72-3.83)	16.6 (7.2-38.3)	98.34 (96.2-99.3)
CIN3 or worse			
RNA-negative	0.31 (0.17-0.57)	3.1 (1.7-5.7)	99.69 (99.4-99.8)
DNA-negative	0.22 (0.10-0.49)	2.2 (1.0-4.9)	99.78 (99.5-99.9)
LBC-negative	0.93 (0.29-3.02)	9.3 (2.9-30.2)	99.07 (97.0-99.7)

DNA, deoxyribonucleic acid; LBC, liquid-based cytology; RNA, ribonucleic acid.
*NPV was estimated excluding the risk among those attending the second round of screening

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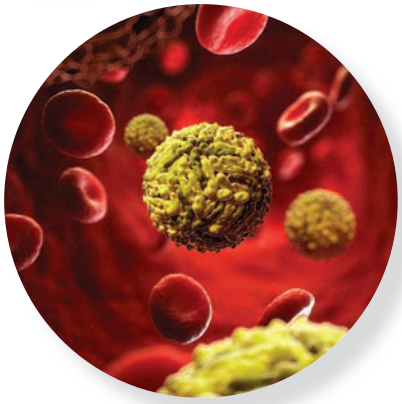

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The combined follow-up in these triple test-negative and test-positive women identified a total of 28 incident CIN3 cases, of which four were detected in triple test-negative women. The combined cumulative risk of developing high-risk HPV-positive CIN3 over six years was 0.22 percent for women who had tested negative with DNA-based screening and 0.31 percent who had tested negative with mRNA-based screening. This non-significant difference translates into an additional risk of CIN3-positive findings of 0.93 percent per 1,000 test-negative women. The longitudinal relative sensitivity of mRNA-based testing compared with DNA-based testing was 91.5 percent for CIN3+, and the negative predictive values were 99.8 percent for the DNA-based and 99.7 percent for the mRNA-based test. Differences between the two molecular tests were not statistically significant, and the high longitudinal negative predictive values for mRNA-based and DNA-based testing suggest that the two testing modalities will both effectively identify women with low risk of developing high grade precursors or cervical cancer.

However, the improved specificity reported with mRNA-based screening in the baseline study suggests that unnecessary follow-up procedures including treatment following a false-positive finding will be less common with the mRNA-based test. In fact, in the original study, 580 women were referred for colposcopy after DNA-based screening compared with 464 who were referred for colposcopy after mRNA-based screening, with no significant difference in the detection of CIN3+. Thus, mRNA-based testing exhibited high sensitivity for identifying women at risk for or with cervical cancer and good longitudinal safety for women who tested negative over a period of at least five to six years.

Conclusion: the role of mRNA-based HPV testing in cervical cancer screening protocols

In 2018, the U.S. Preventive Services Task Force observed that false positive findings with unnecessary follow-up testing and treatment are chief harms of cervical cancer screening. Implementation of mRNA-based HPV testing offers an opportunity to reduce unnecessary (and costly) follow-up without increasing the number of women who develop cervical cancer or precancerous conditions after a negative test. Long-term data showing strong negative predictive value with the mRNA-based test are reassuring given the recent introduction of extended screening intervals (more than or equal to three years) in some national cervical cancer screening programs.

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Twelve steps to CD4 testing—Part III: Management of opportunistic infections

By Beckman Coulter Life Sciences

The 2016 and 2017 World Health Organization (WHO) guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV, and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection.

While these guidelines recommend lifelong antiretroviral therapy (ART) regardless of CD4 cell count ("treat all policy") and analysis of viral load (VL) as the preferred monitoring approach, they also provide clear guidance on the indispensable role of CD4 in assessing baseline risk of disease progression—particularly for individuals presenting with advanced disease—decisions regarding starting and stopping prophylaxis for opportunistic infections (OIs), and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

As a recap, the following is a continuation from last month's "HIV treatment." We now continue with "Management of opportunistic infections."

7. PROPHYLAXIS INTERVENTIONS

Prophylaxis interventions for people with advanced HIV disease

Co-trimoxazole (CTX) prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a **CD4 count <350 cells/µl.**[10,11]

Co-trimoxazole prophylax is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a **CD4 count <350 cells/µl.**[10,11]

Pre-emptive antifungal therapy: In adults and adolescents, if blood cryptococcal antigen screening positive among people with **CD4 counts <100 cells/µl** (where lumbar puncture is negative or not feasible or if lumbar puncture excludes cryptococcal meningitis).[12]

Recommendations for the package of prophylaxis interventions for people with advanced HIV disease[11]

Intervention: Co-trimoxazole prophylaxis		
INDICATIONS TO START	Adults	Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count <350 cells/ mm3. *Strong recommendation, moderate-quality evidence* Malaria and/or severe bacterial infections highly prevalent: co-trimoxazole, prophylaxis should be initiated regardless of CD4 cell count or WHO stage. *Conditional recommendation, moderate-quality evidence.*
	Adolescents	Same as children
	Children	Regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage, those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 count ≤350 cells/mm3. *Strong recommendation, high-quality evidence*
INDICATIONS TO STOP	Adults	Clinically stable on ART, with evidence of immune recovery and viral suppression. *Conditional recommendation, low-quality evidence* Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage. *Conditional recommendation, moderate-quality evidence.*
	Adolescents	Same as children
	Children	High prevalence of malaria and/ or severe bacterial infections: continued regardless of whether ART is provided. *Conditional recommendation, moderate-quality evidence* Low prevalence of malaria and/ or severe bacterial infections: discontinued for children who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 cell count >350 cells/mm3. *Strong recommendation, very-low-quality evidence*

11.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, pages 35-37.

8. MANAGEMENT OF OPPORTUNISTIC INFECTIONS

Identification of opportunistic infections: Tuberculosis (TB)

Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill, **urine lateral flow (LF)-LAM** should **not** be used for the diagnosis of TB.[12]

LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a **CD4 count less than or equal to 100 cells/µl**, or people living with HIV who are seriously ill, regardless of CD4 cell count or with unknown CD4 cell count.[12] LF-LAM should not be used as a screening test for active TB.[12]

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- *Trichomonas vaginalis*

Bacterial Vaginosis
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- *Gardnerella vaginalis*
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UMM
- *Ureaplasma spp*
- *Mycoplasma genitalium*
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Intervention:

Pre-emptive anti-fungal therapy: fluconazole 800 mg/ day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day

INDICATIONS TO START	**Adults**	Blood cryptococcal antigen screening positive among people with CD4 counts <100 cells/mm3 (where lumbar puncture is negative or not feasible or if lumbar puncture excludes cryptococcal meningitis) a *Conditional recommendation, low-quality evidence*
	Adolescents	Same as adults
	Children	Not applicable since screening is not recommended
INDICATIONS TO STOP	**Adults**	If HIV viral load monitoring is not available: When people are stable and adherent to ART and receiving antifungal maintenance therapy for at least one year and have a CD4 cell count ≥200 cells/mm3 (two measurements six months apart). *Strong recommendation, low-quality evidence* If viral load monitoring is available: When people are stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count ≥100 cell/mm3 (two measurements six months apart) and a suppressed viral load. *Conditional recommendation, low-quality evidence*
	Adolescents	Same as adults b
	Children	Not applicable since screening is not recommended

11.) World Health Organization (2017): Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, pages 35-37.

Identification of opportunistic infections: Cryptococcus spec.

The use of routine serum or plasma Cryptococcus antigen (CrAg) screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:[13]

a. patients with a **CD4 count less than 100 cells/µl**; and

b. where this population also has a high prevalence (>3 percent) of cryptococcal antigenaemia.

Identification of opportunistic infections: Skin and oral conditions

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's **CD4 count declines below 200 cells/µl**. As a result, skin and oral conditions affect up to 90 percent of adults and children with HIV in resource-limited settings.[14]

Certain systemic diseases, such as Kaposi sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance, and psychological stress. In the case of candidiasis, it can cause pain on swallowing, limiting a person's ability to take ARV drugs.[14]

9. VACCINATION SCHEMES

Vaccination Scheme: Measles

Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, **notably when the CD4 count is above 200 cells/µl**.[14] People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines.[14]

Vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV and should be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to WHO definitions **(CD4 cell counts < 50 cells/µl)**.[15]

Vaccination Scheme: Yellow Fever

Yellow fever vaccine may be offered to asymptomatic people living with HIV with **CD4 cell counts >200 cells/µl**; it is therefore contra-indicated in people with advanced HIV disease until they achieve a CD4 cell count ≥200 cells/µl. Although the data on the safety and immunogenicity of yellow fever vaccine when used among children living with HIV are limited, yellow fever vaccine may be administered to all clinically well children. HIV testing is not a prerequisite for vaccination.[15]

This is the last MLO Special Feature outlining Beckman Coulter Life Sciences' technical overview of "12 Steps to CD4 Testing." For more information, visit https://www.beckman.com/about-us/cares/initiative.

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Navigating a successful laboratory automation implementation

By Harold D. Lanzoni and Tracy Steffen

Image Courtesy of Roche Diagnostics

By simplest definition, implementing laboratory automation involves the conversion from analog to technology-based solutions with the objectives of streamlining processes, increasing efficiencies, reducing errors, and improving overall workflow. The degree to which the conversion can be deemed successful is dependent upon three key factors: 1. effective change management, 2. lab and IT staff collaboration, and 3. consistent leadership before, during, and after implementation occurs.

Why automation?

As labs continue to grow larger in size through consolidation, and staffing resources simultaneously shrink due to high attrition and retirement rates, automation is quickly becoming a necessity for facilities that want to remain profitable in a highly competitive marketplace. Laboratorians who resist the concept of automation may very well find their operations lagging behind the curve as their counterparts outpace them in terms of quality and productivity.

Consolidation trends show no signs of slowing, leading to the creation of more high-volume and core labs. This creates a larger workload for fewer people to manage, supporting the need for automation in order to keep up with volume.

Now more than ever, labs are being challenged to meet increasingly stringent performance expectations that aren't always attainable through increased staff effort or general process improvements. Automation affords lab management the capability to help meet this growing demand. While it may not necessarily produce faster test turnaround times (TATs)—a key performance metric for many labs—automation does go a long way toward enabling reproducible TATs, which can contribute to improved clinician satisfaction.

The potential benefits of automation go well beyond consistent TATs, extending into improved test result reliability, cost and time savings, streamlined processing, and greater quality performance. Perhaps most importantly, automation can enable the clinical lab to make a bigger contribution to the overall goal of better patient care, offering empirical evidence that demonstrates the lab's value to healthcare system administrators.

So, what is it that specifically determines and drives an effective implementation? Every laboratory has its own unique set of needs and challenges, but generally speaking, success at many labs seems to hinge upon three critical elements.

1. Change management

Thoughtful change management is absolutely essential to prepare and support individuals and teams through an effective changeover to automated processes.

Good communication is key. Change management efforts should begin as soon as the decision to automate is confirmed by communicating information to all internal and external stakeholders who will be impacted by the implementation. This includes not only lab staff and managers, but other departments and teams as well. For instance, implementation may necessitate changes to barcode labeling and other related processes, or it might create the need to revisit sample collection procedures. To smooth the transition, it's important to convey all relevant updates and information on a timely basis, and to keep the lines of communication open throughout and after implementation to minimize the potential for conflicts to arise.

Resistance to change is a commonly seen issue in the clinical lab setting, and the prospect of implementing new automated processes can invoke a sense of fear and trepidation among some staff members. The transition to automation may require some laboratorians to undergo a critical shift in thinking and work approach. One of the biggest challenges that implementation presents is an underestimation of the need for the softer-skills aspects of change management. Data-driven laboratorians who readily understand the technical aspects of their jobs such as analytics, correlation, and validation efforts may be resistant to embrace the major paradigm shift that automation entails, fearing these new technologies will render their roles obsolete.

Reassurance that includes the rationale for and benefits of switching over to automation can go a long way toward overcoming objections, easing fears, and creating buy-in among hesitant laboratorians. It's also worth pointing out that automation can actually free up lab staff from the constraints of time-consuming routine process steps to focus on higher-value tasks.

Additionally, the automation implementation process can provide a valuable opportunity to review the lab's current design and layout to look for areas where process improvements may be warranted. Automation can quickly reveal any inefficiencies and weaknesses that need to be addressed in the overall workflow. New interim procedures may need to be instituted during the transitional phase of implementation, and staff should be made aware that it can take some time and tweaking before peak automation efficiency is achieved. It is essential to engage staff during these process re-mapping exercises, as they are the people who understand the laboratory's workflow better than anyone.

2. Information technology

The very foundation of automation is deeply rooted in state-of-the-art technology, putting IT departments in a vital position to help accomplish a successful implementation. The automation vendor and the lab manager should each identify what role their own IT staff will play early in the pre-sale process, addressing current status, all supportive measures the proposed solution will require, and any resources that can be made available. It is usually incumbent upon the vendor to identify the lab's IT capabilities through discussions regarding the automation solution, but the lab manager and staff must also gain a firm understanding of the supports and tools they will need to provide on their end to facilitate the implementation process.

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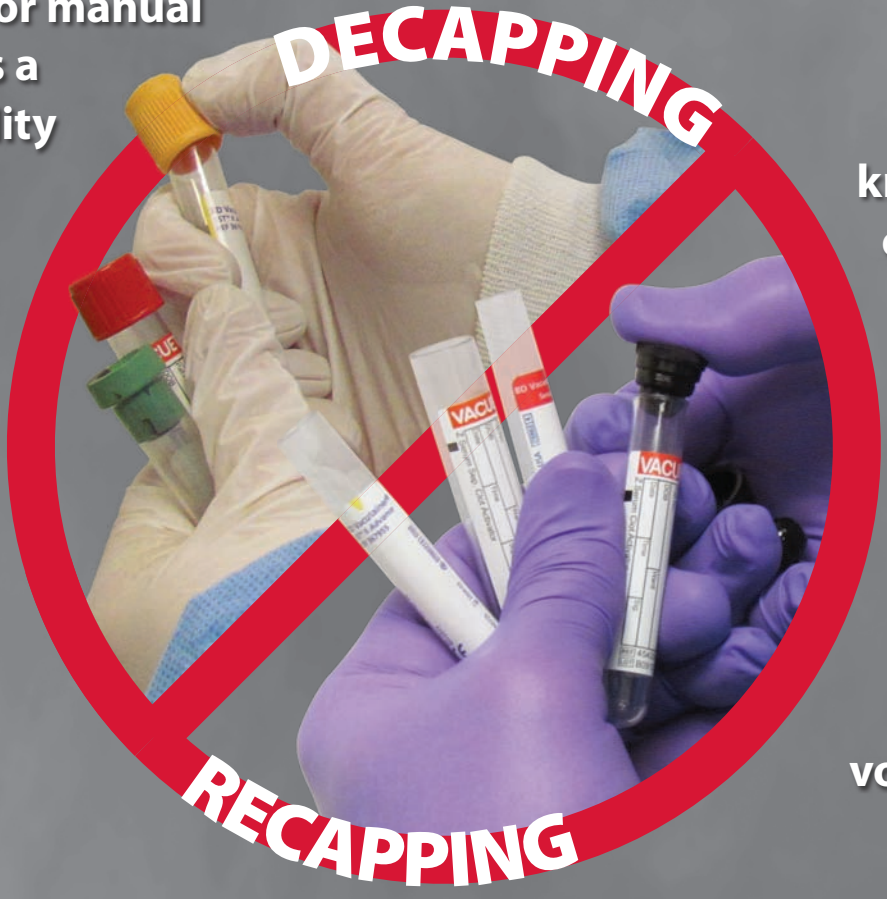

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The laboratory and vendor IT staff should plan to work together as a team to achieve the best automation results possilble. Often, the automation vendor can provide training throughout the implementation that will teach the lab's own IT department how to offer optimal support after go-live and into post-implementation activities.

Recognize that, while automation systems often employ highly sophisticated features and functionalities, certain labs may not be able to leverage the full capabilities of the system due to limitations of their laboratory information systems. For this reason, labs should reasonably assess which solutions are the most practical and realistic for their organizations considering their own capacities and capabilities. Vendors may be able to present ideas focused on overcoming obstacles and helping create feasible workarounds wherever possible.

3. Leadership teams

All key players are important during the conversion to automation, but the success of any team effort depends heavily on its management and leadership. Viewing the implementation solution as a total symbiotic system and not just the collection of individual components (automation, chemistry analyzers, hematology platforms, etc.) is a helpful mindset to maintain.

Developing a lean-dedicated leadership team that can effectively function to see the implementation process through from start to finish helps to dissolve silos and fosters a collaborative atmosphere in which everyone involved in the implementation is invested in its success. The leadership team should be comprised of representatives from across the lab and throughout the disciplines that are directly impacted by the solution, such as processing, chemistry, hematology/coagulation, and any others.

The takeaway

While automation may sometimes seem like a magic wand with the power to transform the lab into a perfect, error-free facility at the flip of a switch, keep in mind that technology is only as effective as the people who manage it. It helps to think of automation as a tool with the potential to help lab staff do their jobs better and optimize efficiency; human input is still required to drive the result.

Ultimately, automation is intended to enhance the skills and value of human staff, not replace them. Thus, the onus is on automation vendor partners to create reasonable expectations for laboratory staff, and to provide support during and after the implementation to continuously monitor the outcome and make ongoing adjustments as needed to ensure long-term success. Conversely, it is the responsibility of lab management to foster a culture of continuous improvement so that the tools, processes, and staff are enabled and empowered to adapt to inevitable changes in the lab.

Harold D. Lanzoni serves as a Strategic Workflow Consultant with **Roche Diagnostics** who brings 30 years of laboratory experience and Lean/Six Sigma principles to his consultations with clinical labs. He works with labs to identify opportunities and strategies to improve operational efficiency and quality.

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A dialogue with AABB President, Dr. Michael Murphy

Congratulations on your new position! How did you first hear about AABB and when did you become a member? Thank you. It is a great honor for me to be the next President of AABB and to continue advancing the association's vision of making transfusion medicine and cellular therapies safe, available, and effective worldwide. I first heard about AABB when I was training as a hematologist in the mid-1980s. I became aware of the AABB scientific journal, *TRANSFUSION*, and the AABB Annual Meetings. I attended my first meeting in Los Angeles in 1990 to present some research work from our group and became an AABB member the same year.

Why did you choose hematology? I trained as a general physician in London and decided to do specialist training in hematology—I was attracted by the possibility of combining clinical and laboratory work with research. I then became interested in transfusion medicine when managing the transfusion problems of patients with hematological malignancies.

Which areas of transfusion medicine interest you the most? I continue to work as a hospital hematologist, therefore, the issues of hospital transfusion practice remain my focus. I am interested in the use of information technology to improve the safety and appropriateness of transfusion practice by ensuring that patients receive the correct blood, and support clinicians to make good decisions about the use of blood. I am also involved in clinical research to provide the evidence for improving transfusion practice and the use of alternatives to transfusion.

What is the public's biggest misconception about blood banking? I think the public needs to be better informed to better understand the risks and benefits of transfusion and the importance of blood donation. Blood has a limited shelf life and regular blood donations are fundamental to ensure that the blood supply remains adequate. In case of disaster—natural or manmade—it is the blood that is already on the shelves that saves lives.

Blood can only be stored safely for up to 42 days and platelets last only five days. What efforts are being made to extend the shelf life of blood products? There is no doubt that a limited shelf life for cellular blood components like red blood cells and platelet units is a significant challenge for blood suppliers and hospitals in terms of supply and minimizing wastage. There has been recent debate about the potential risks associated with stored red blood cell transfusions, but a number of high-quality clinical trials have not confirmed this effect. There is ongoing research into methods to allow safe extension of the shelf life of red blood cell units using new storage solutions and conditions. The concern about extended storage of platelet units is bacterial contamination as these products are stored at 22 °C, and there is research into new storage solutions to allow extension of the shelf life beyond five days. There is also considerable interest in storing platelets at 4 °C, the same temperature as for storing red blood cell units, because of some evidence of their superior immediate hemostatic effect.

What is trending in the field of umbilical cord blood banking? Cord blood has unique attributes that make it the stem cell source of choice for many pediatric patients, and those who cannot find a well-matched adult donor. However, the need for double unit transplants to achieve a sufficient cell dose has significant cost implications, and haplomismatched donations from family members are being used increasingly instead of cord blood. To overcome the limiting number of stem cells in cord units, several ex vivo expansion protocols have been developed and are now in clinical trials. Moving beyond cord blood itself, umbilical cord and placental tissues have proven to be advantageous sources of mesenchymal stromal cells whose immunoregulatory and regenerative properties are being tested in a wide range of clinical applications.

Extreme blood loss is the most common cause of death on the battlefield, accounting for 90 percent of fatalities. What relationship does AABB have with the military? AABB has close ties with the Armed Services Blood Program (ASBP), which provides blood products for service members and their families, both in the U.S. and internationally. ASBP blood collection centers are AABB-accredited and follow AABB standards that promote donor and patient safety. We also hold an annual workshop with the THOR (Translational Hematology and Oncology Research) network that helps to translate lessons from the battlefield to civilian care.

What is a typical day in the office like for you? Being a morning person, I like to make an early start and that is a challenge for me toward the end of the U.K. working day, since it is still early afternoon or even morning in the U.S. Some early mornings involve teaching of residents followed by daily transfusion rounds in the blood bank with our transfusion team to review any transfusion problems. We also review the transfusions from the previous day, which have triggered an alert on our electronic decision support process and which need to be followed up with the doctor who made the order. The rest of the day will be taken up with meetings with our transfusion team and clinical fellows to review progress with quality improvement initiatives and research projects. Toward the end of the day comes AABB business and conference calls, and if there is time I will relax with a session in the gym or a gentle run before heading home.

What type of career path would you recommend for students wanting to pursue a career in transfusion medicine? The traditional route for medical staff into transfusion medicine is through pathology, but alternative career paths are now possible including anesthesiology, emergency medicine, or critical care medicine. The field of transfusion medicine is being strengthened by specialists from varied medical backgrounds.

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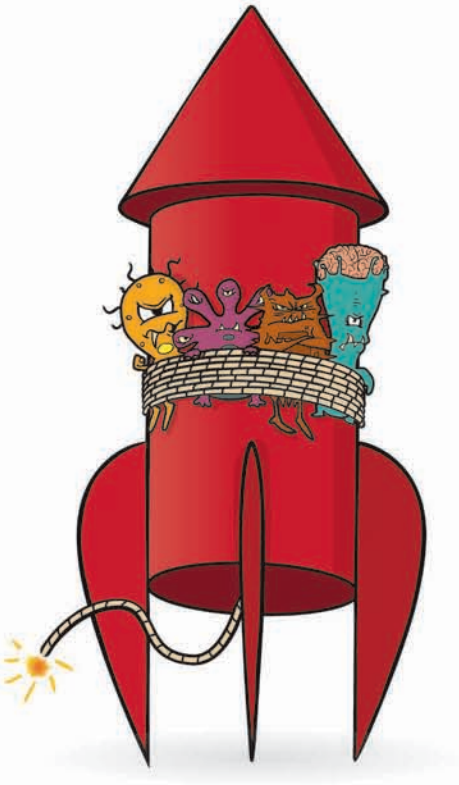

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