Chapter 15
Personalized Therapy of Infectious Diseases

Introduction

Personalized approach involves selection of an appropriate treatment right from the start for optimal effectiveness and for reduction of development of drug resistance. Advances in point-of-care (POC) diagnostics have enable physicians to avoid dispensing antibiotics for viral infections and fevers of unknown origin. Improved diagnostics can enable prescriptions according to a pathogen’s susceptibilities.

Various examples of personalized management are given with emphasis on HIV, which was one of the first among infectious diseases where molecular diagnostic was used to guide treatment. Molecular diagnostics has been refined by nanobiotechnology and combined with refinements in formulation and delivery of antimicrobial agents for personalized management of infectious diseases.

Genetic Susceptibility to Infections

Several monogenic inborn errors of immunity are now known to underly resistance or susceptibility to specific infections. The monogenic component of the genetic theory provides a plausible explanation for the occurrence of severe infectious diseases during primary infection. Over the last 20 y, increasing numbers of life-threatening infectious diseases striking otherwise healthy children, adolescents, and even young adults have been attributed to single-gene inborn errors of immunity. Infectious diseases typically manifest as sporadic traits because human genotypes often display incomplete penetrance (most genetically predisposed individuals remain healthy) and variable expressivity (different infections can be allelic at the same locus). Infectious diseases of childhood, once thought to be archetypal environmental diseases, may be among the most genetically determined conditions of mankind (Casanova 2015). This should be taken into consideration in personalized approach to management of infections.

Like the concept of personalized medicine based on patients’ genetic differences, treatment of infectious diseases involves individualizing therapy according to genetic differences in infectious agents. Treatment of infectious diseases genetic susceptibility of the patient.

Personalized Use of Antibiotics

Antibiotics are usually described as specific against certain microorganisms and selection is often made after identification of the microorganism. Sensitivity is also determined by culture of the microorganism in presence of antibiotic. Optimal use of antibiotics is dependent on the identification of primary and secondary focus, and knowledge on which pathogens to expect in a specific infectious syndrome and information on general patterns of regional antibiotic resistance. Furthermore, sampling for microbiological analysis, knowledge of
patient immune status and organ functions, travel history, pharmacokinetics and -dynamics of the different antibiotics and possible biofilm formation are among several factors involved in antibiotic therapy of infectious diseases, which provides the possibility of personalization by choosing the parameters that lead to the most relevant antibiotic therapy for that specific patient (Moser et al. 2019).

**Personalized Management of Sepsis**

Sepsis can be caused by bacteria, fungi or viruses and the term is used when the response to the infection is inadequate and may lead to organ dysfunction. There is no specific treatment; its management basically focuses on containing the infection through source control and antibiotics plus organ function support. Personalized medicine approach based on use of biomarkers can identify individuals who are likely to benefit from more specific treatments.

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells characterized by their immunosuppressive functions, which are barely detectable in healthy persons, but expand during inflammatory conditions. MDSCs play an important role in the pathogenesis of infectious diseases along with sepsis and all clinical studies to date suggest that high proportions of blood MDSCs are associated with clinical worsening and rise of incidence of nosocomial infections as well as mortality (Schrijver et al. 2019). Therefore, MDSCs are biomarkers and therapeutic targets personalized medicine and precision immunotherapy for patients suffering from sepsis. Blocking MDSC-mediated immunosuppression and trafficking or depleting of MDSCs might improve outcome of sepsis.

**Personalized Management of Viral Infections**

A schematic approach to integration of antiviral strategies for personal management of viral diseases is shown in Fig. 15.1.

**Management of HIV**

There are two variable factors in HIV/AIDS: how people respond to the HIV and how HIV responds to drugs.

**CD4 Counts as a Guide to Drug Therapy for AIDS**

When patients are infected with HIV/AIDS, the number of circulating CD4 T-cells drops significantly. CD4 counts assist in the decisions on when to initiate and when to stop the treatment, which makes this test so important. While such testing is routine in Western countries and used repeatedly over the course of treatment to see if interventions are effective it is unavailable to many people in the developing world, especially in rural areas. A cheap test for CD4 plus T lymphocytes in the blood is in development using biosensor nanovesicles to enhance the signal.

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**Fig. 15.1** An integrated approach to viral diseases. (© Jain PharmaBiotech)
Drug-Resistance in HIV

Although antiretroviral drugs are highly effective in reducing viral replication and have significantly reduced death rates from the AIDS in the US, drug resistance threatens their utility. Despite the availability of over numerous anti-HIV drugs, up to 50% of the patients on combination therapy experience treatment failure mainly due to development of resistance to the drugs. The rational selection of combinations of drugs to avoid or overcome resistance is one of the critical challenges to achieving long-term viral suppression and optimal clinical outcome in HIV/AIDS. The cause of resistance is extremely complex, because over 100 individual mutations in the HIV genetic code known to be involved. The following indicates clinical utility of genotyping:

- Drug resistance mutations are independent markers of virologic failure.
- Treatment failure does not indicate failure of all drugs in a combination.
- Provides information about cross-resistance.

Drug-resistance testing Assays for drug resistance testing in HIV-1 infection are now available and clinical studies suggest that viral drug resistance is correlated with poor virologic response to new therapy. The clinical utility of genotyping was established in 4 studies in 1999 using TRUGENE HIV-1 Genotyping Kit and the OpenGene System (Visible Genetics Inc). The first study, VIRADAPT (antiretroVIRal ADAPTation), was conducted by researchers from the Centre Hospitalier at the Universitaire de Nice in France. Six-month data from VIRADAPT demonstrated that drug selection based on genotyping was effective in producing a statistically significant benefit in lowering the viral loads of HIV patients who were failing triple drug combination therapy. Results from the second prospective study in 2000, sponsored by the NIH, “Genotypic Antiretroviral Resistance Testing (GART)”, demonstrated the clinical utility of genotyping in the treatment and management of HIV/AIDS patients. In the NARVAL study, the largest prospective resistance testing study, HIV-infected patients who received HIV drug resistance genotype testing achieved a better long term virologic benefit versus those patients who received standard of care treatment or phenotypic testing. Results from the HAVANNA study – a 6-month, randomized, prospective, multicenter study involving HIV-positive, heavily pre-treated HIV patients – reported that genotypic testing was of significant benefit as compared to standard of care treatment. Other studies have shown that genotypic sequencing for drug-resistant strains of HIV can guide the choice of antiretroviral therapy and is cost-effective. Celera Diagnostics markets a comprehensive HIV drug resistance test, the ViroSeq HIV Genotyping System. It has proven broad spectrum efficacy in typing all major global subtypes of the virus.

HIV drug resistance genotyping enables HIV-infected patients to be matched with effective antiretroviral drugs and is an essential component of HIV patient management, but currently available testing options are insufficiently sensitive and cost-prohibitive for low- and middle-income countries. Resistance testing is recommended to help guide the choice of new regimens after treatment failure and for guiding therapy for pregnant women. It should be considered in treatment-naive patients with established infection but cannot be firmly recommended in this setting. Testing also should be considered prior to initiating therapy in patients with acute HIV infection, although therapy should not be delayed pending the results. Expert interpretation is recommended given the complexity of results and assay limitations.

Aldatu Biosciences has developed Pan-Degenerate Amplification and Adaption (PANDAA™), a simple, low-cost, highly sensitive method for HIV drug resistance detection with multi-parameter superiority to currently available commercial genotyping options. PANDAA™ enables an already low-cost and sensitive genotyping technology, real-time qPCR, for HIV genotyping by overcoming challenges associated with the biology of HIV, ie; (1) detects drug-resistant HIV variants with >99% sensitivity; (2) is HIV subtype-independent; (3) is multiplexed to simultaneously quantify resistance at multiple genomic positions; and (4) quantitative detection using a calibrator probe measures total HIV RNA and serves as a confirmatory viral load test. PANDAA™ HIV6 – a
thermostable, sample-in/answer-out kit identifies 6 clinically actionable HIV mutations found in >95% of patients failing a WHO-recommended first-line regimen to radically improve HIV treatment cost-efficiency by empowering clinicians to make informed therapeutic decisions and assign the most effective ART regimens at the lowest achievable cost.

Drug susceptibility testing To assess the value of phenotypic drug susceptibility testing as a predictor of antiretroviral treatment response in HIV-infected people, drug susceptibility testing has been performed retrospectively on plasma samples collected at baseline in a cohort of antiretroviral-experienced, HIV-infected people experiencing treatment failure and initiating a new antiretroviral treatment regimen. In multivariate analyses, phenotypic susceptibility is an independent predictor of time to treatment failure with reduced drug susceptibility cut-offs defined as 4.0-fold and 2.5-fold higher than reference virus values. Previous protease inhibitor experience is also a significant independent predictor. Notably, prediction of drug susceptibility based on treatment history alone is not predictive of time to treatment failure. Phenotypic testing results enhance the ability to predict sustained long-term suppression of virus load. PhenoSense HIV (Monogram Biosciences) is a rapid, sensitive, and comprehensive phenotypic drug susceptibility assay for HIV-1 that directly measures the susceptibility, or resistance, of a patient’s virus to all currently available antiretroviral drugs (reverse transcriptase and protease inhibitors). HIV replication capacity, as measured by the PhenoSense HIV assay, may be an additional predictor of clinical outcome and may complement other laboratory parameters, such as viral load and CD4 cell counts, in making individualized antiretroviral treatment decisions, especially for patients experiencing failure of their treatment regimen.

Genetics of Human Susceptibility to HIV Infection

Humans are not equal in terms of susceptibility to infection to HIV, or in the rate of disease progression. This is evidenced by the identification of individuals that remain seronegative despite of multiple exposures to HIV-infected partners, and by the existence of the so called “long-term progressors”. Currently used research approaches include:

- Analysis of the differences of susceptibility at the cellular level. This requires the characterization of the cellular permissiveness to HIV or HIV-derived lentiviruses.
- Mapping of chromosomal susceptibility loci by genome scan using linkage analysis in the in vitro setting of transduction of immortalized B cells from multigeneration families.
- Whole genome association study on a characterized population providing data on viral set-point after HIV seroconversion. This is a collaborative European project supported by the Center of HIV/AIDS vaccine immunology/NIH (CHAVI).

CHAVI is a significant component to the Global HIV Vaccine Enterprise, which includes investigators from institutions across the globe with the goal of solving major problems in HIV vaccine development and design. CHAVI’s initial mission is to find out what the immune system does during HIV infection - including in the rare individuals who control the infection on their own – and try to produce a vaccine to mimic those responses. Work will provide a unique description of how host genetic variation influences the early stages of HIV infection, the exposed and uninfected state, and the interindividual differences in the generation of neutralizing antibodies or in breath of cytotoxic T lymphocyte responses. The project will apply state of the art genome association studies.

The Host Genetics Core, which includes the EuroCHAVI project, will use whole genome analysis to analyze the differences in host genetic structures that indicate susceptibility to HIV-1 transmission and/or infection. EuroCHAVI aims to quickly identify common genes that affect how the body responds to HIV and the speed at which the infection progresses to AIDS. Whole genome analyses are carried out using the Infinium™ HumanHap550 Genotyping BeadChip Illumina technology. This Chip addresses more than 555,000 SNPs providing comprehensive genomic coverage across multiple populations. This large-
scale genome analysis is critical for determining the role of genetic variants in a complex disease such as AIDS.

**Measurement of Replication Capacity**

HIV-1 uses the CD4 cell surface receptor and one of two co-receptors (CCR5, CXCR4) to infect cells. A switch from the CCR5 to the CXCR4 co-receptor is associated with more rapid disease progression and death from AIDS related illness. Replication Capacity (Monogram Biosciences) provides an important measure of the ability of HIV to proliferate and is currently offered with Monogram Biosciences’ PhenoSense and PhenoSense GT. Genetic changes (mutations) in HIV that confer drug resistance often impair the virus’ ability to replicate efficiently and lead to reductions in replication capacity. Several clinical studies have found that patients experiencing treatment failure do not progress to AIDS if the drug resistant virus has impaired replication capacity. These findings support the use of RC measurement as a tool for the management of HIV infection and to help individualize treatment regimens. A follow up study has demonstrated that the emergence of CXCR4 virus variants independently predicts immune system deterioration and HIV disease progression.

A proportion of the variation in HIV-1 viral load in the infected population is influenced by host genetics. Using a large sample of infected individuals with genome-wide genotype data, a study has mapped genomic regions that influence HIV viral load to quantify their impact (McLaren et al. 2015). The authors identified amino acid positions located in the binding groove of class I HLA proteins (HLA-A and -B) and SNPs in the chemokine (C-C motif) receptor 5 gene region that together explain 14.5% of the observed variation in HIV viral load. Controlling for these signals, they estimated that an additional 5.5% can be explained by common, additive genetic variation. Thus, they demonstrate that common variants of large effect explain most of the host genetic component of HIV viral load. This study suggests that analyses in non-European populations and of variant classes not assessed by GWAS should be priorities for this field going forward.

**Personalized Vaccine for HIV**

A vaccine made for the individual patient, instead of an off-the-rack treatment, is based on dendritic cells which are removed from each HIV-infected patient and subsequently multiplied in vitro. By priming the immune system, as with a vaccine, to fight the specific strain of HIV/AIDS infecting a given patient, this would be a more effective weapon against the virus than the antiretroviral cocktails currently in use. Not only were there few reported side-effects from the personalized vaccine in clinical trials, but the researchers also measured increased levels of CD8-lymphocytes in the patients thus confirming that the intervention was targeted and controlled (Routy et al. 2010).

AC-3S, another therapeutic vaccine, is made up of a highly conserved HIV-gp41 motif coupled with the CRM197 carrier protein, and high levels of anti-3S antibodies (Abs) have been associated with improved protection of CD4+ T cell survival. Safety of VAC-3S was demonstrated in a phase I trial. A multicenter, randomized, double-blind, placebo-controlled phase II clinical trial on HIV-1-infected patients under ART therapy was well tolerated with no serious adverse events and induced a significant increase in anti-3S Ab response in vaccinated patients compared to placebo (Vieillard et al. 2019). In high responders, the robust increased of CD4 count was associated with a significant and sustained reduction of PD-1 expression on CD4+ T cells, which was correlated with level of anti-3S Abs. The findings of increase of non-exhausted CD4+ T cells are important for personalized HIV vaccination for HIV-infected patients with high level of PD-1 to improve their T cell immune function.

**Prevention of Adverse Reactions to Antiviral Drugs**

Efavirenz is commonly a component of drug cocktails used to fight HIV, but it can cause neurological adverse reactions such as disturbing dreams and dizziness. A genetic mutation in the gene for CYP2B6, which occurs in 20% of blacks but only 3% of whites, slows the drug metabolism and nearly triples the average blood concentration of the drug. Therefore, the odds that
people taking efavirenz will suffer side effects that lead them to discontinue the treatment will be higher. Patients with this mutation should start therapy with a low dose of efavirenz. Another factor that affects the drug metabolism is body weight. Heavier persons tend to metabolize efavirenz relatively quicker than those with lower weights. Patients who clear the drug very rapidly may show lack of efficacy of the drug. Personalized approach to therapy would take these variations into consideration. Genotyping could predict the response to therapy regardless of the racial difference.

QIAGEN introduced a SSP© PCR assay to type the HLA-B*5701 allele, a genetic variation in the HLA system. HIV patients carrying the HLA-B*5701 biomarker have a 60% higher risk to develop hypersensitivity reaction (HSR) to Abacavir, which is a component of several marketed drugs inhibiting the reverse transcriptase of HIV. HSR is a serious and sometimes even fatal multi-organ syndrome that manifests by fever, respiratory or constitutional symptoms. The FDA has already advised healthcare professionals that all HIV patients should be screened for HLA-B*5701 before initiating treatment with drugs containing Abacavir. Health authorities in other countries have issued similar warnings in response to the PREDICT1-1-Study, which found that HLA-B*5701 is a major biomarker for the HSR. The screening for HLA-B*5701 prior to Abacavir treatment allows the identification of patients likely to develop HSR. Using HLA-B*5701 tests as a companion diagnostic with the drug Abacavir, therefore, helps to better protect HIV-infected patients in treatment from severe additional suffering. The combination of diagnostics and therapeutics is a key approach to eliminating risks of side effects and therefore increasing the efficacy of drugs.

Pharmacogenetics and HIV Drug Safety

Pharmacogenetics could benefit HIV therapeutics because of the high prevalence of drug-related adverse events and the long-term nature and complexity of combination therapy. There are several pharmacogenetic determinants of antiretroviral drug exposure, toxicity, and activity. Studies across the world have consistently demonstrated that HLA-B*5701 predicts the likelihood of hypersensitivity reactions to abacavir. As a result of these findings, pharmacogenetic screening for HLA-B*5701 has entered routine clinical practice and is recommended in most guidelines before starting an abacavir containing regimen. A novel HLA-B*57:01 screening test has been described, which can be easily implemented by those laboratories already involved in the detection of viral load and virus genotyping (Russo et al. 2011).

Several prospective clinical trials and cohort studies have identified several associations between human genetic variants, drug metabolism and toxicity. These include nevirapine hypersensitivity and hepatotoxicity, efavirenz plasma levels and central nervous system side effects, indinavir- and atazanavir-associated hyperbilirubinemia, antiretroviral drug-associated peripheral neuropathy, lipodystrophy and hyperlipidaemia, NRTI-related pancreatitis, and tenofovir-associated renal proximal tubulopathy. Thus, pharmacogenetics is expected to play an important role in HIV treatment in the future.

Pharmacogenomics of Antiretroviral Agents

Several drugs with different mechanisms of action are available for the treatment of HIV. None of them is curative and there is considerable variation in the response to antiretroviral drugs among individuals. This concerns both the interindividual differences in pharmacokinetics, and in toxicity. Various research approaches are currently used are:

- Analysis of genetic variation in CYP450 and transport genes.
- Analysis of genetic variation in mitochondrial genes and lipid metabolism and transport genes to investigate the basis of metabolic and lipid disorders associated with use of specific antiretroviral agents.

A growing number of entry inhibitors are under clinical development, with some already approved. With the emergence of virus strains that are largely resistant to existing reverse tran-
scriptase and protease inhibitors, the development of entry inhibitors comes at an opportune time. Nonetheless, because all entry inhibitors target in some manner the highly variable Env protein of HIV-1, there are likely to be challenges in their efficient application that are unique to this class of drugs. Env density, receptor expression levels, and differences in affinity and receptor presentation are all factors that could influence the clinical response to this promising class of new antiviral agents.

SensiTrop test (Pathway Diagnostics) is a molecular-based assay for co-receptor tropism that helps physicians to personalize HIV therapy. It will identify the patients being treated for HIV infection that will benefit from entry inhibitor drugs. Quest Diagnostics has licensed the heteroduplex tracking technology used in SensiTrop test and is developing a validated test based on this.

**Role of Diagnostic Testing in Management of HIV**

Role of diagnostic testing in management of patients with HIV infection is as follows:

- Detection of HIV-infected individuals
- Evaluation of newly diagnosed patients
- Monitoring of therapeutic regimens
- Prognosis of disease progression (CD4 plus viral load)
- Management of drug resistance
- Prevention of adverse reactions to drugs

**Role of Genetic Variations in Susceptibility to HIV-1**

NIH is supporting research projects that will study genetic variations linked to susceptibility for HIV-1 infection and AIDS progression among drug-abusing populations. It also supports research into the effects of viral mutations and recombination associated with drug abuse on host responses to infection, as well as the pharmacogenetics of interactions among HIV-1 treatment medications and either drugs of abuse or therapies used in the treatment of drug addiction. The research should involve chronic users of addictive substances, or use of appropriate in vitro or in vivo models, to improve our understanding of the role of genetic variation within genes involved in modulating immune function, or genes that are highly expressed in monocyte derived dendritic cells, mucosal cells, or other cells/tissues that may alter an individual’s susceptibility to HIV-1 infection. NIH also plans to study whether drugs of abuse such as methamphetamine interact with host or viral genetic factors to either increase HIV-1 susceptibility or diminish the host’s ability to internalize pathogens and subsequently activate T cells.

**Role of Personalized HIV Therapy in Controlling Drug Resistance**

HIV patients are characterized by both the high genomic diversity of the virus, which is unique for each patient and time point. The large number of therapy options makes it difficult to select an optimal therapy, particularly in patients that develop resistance to some drugs. Testing for HIV drug resistance in drug-naive individuals and in patients in whom ART is failing, and the appreciation of the role of testing, are crucial to the prevention and management of failure of ART (Günthard et al. 2019). Computer-based therapy selection, which assesses the level of viral resistance against drugs, has become a mainstay for HIV patients as shown in Fig. 15.2.

**PhenoSense® to Test HIV Drug Resistance**

PhenoSense® GT (Monogram Biosciences/LabCorp) is a resistance test that combines three tests – PhenoSense® HIV, GeneSeq® HIV and Replication Capacity (RC) – to make up one complete picture of drug resistance. The combination test is performed from the same blood sample and the results are in one report. PhenoSense® GT looks at an individual’s HIV using two different methods, so that the most effective treatment can be selected. It is a direct measure of the virus’ ability to replicate in given concentrations of antiviral compounds as measured by the phenotypic portion of PhenoSense® GT. The patient virus is also sequenced, with the
genotypic data provided alongside the susceptibility results. Finally, it measures the ability of the viral protease and reverse transcriptase to drive replication – known as replication capacity, one component of viral fitness. PhenoSense® GT offers consistent results because both phenotypic and genotypic results come from the same blood sample, and some of the discrepancies between phenotypic measurements and genotypic predictions are resolved as part of the assay.

Fig. 15.2 Workflow of genotypic resistance analysis for personalized HIV therapy. Legend: Workflow of current-day genotypic resistance analysis. The process begins by detecting the viral load (2) in a patient (1). In the case of anticipated therapy change the viral genome is sequenced from the patient's blood serum (3). Interpretations of the viral genome sequence is affected either manually using a mutation table (4a), or via a rules-based system (4b), or with a statistical model derived from clinical resistance data (4c). The interpretation results in a resistance profile (5) that is qualitative in the first two cases and quantitative when using statistical models. The physician uses this profile to select a therapy (9). In doing so, additional information on the patient is also considered (patient history, habits, drug side effects, etc (6). Therapy prediction engines (7) can assist this process by a quantitative analysis that yields a list of therapies ranked by their likelihood of success (8). (Modified from: Lengauer et al. 2014)

Sequencing for Detecting Mutations to Personalize HIV Therapy

According to work being done at the US National Institute of Allergy and Infectious Diseases, long-read sequencing can enable researchers to not only detect what drug-resistance mutations are present in someone with HIV, but also whether those mutations are present in one strain or spread across multiple strains of the virus circulating in that patient. Sanger sequencing is currently used to detect drug resistance mutations in HIV, but the sensitivity of this approach limits its ability to perceive minor mutations. Although NGS improves upon that sensitivity to detect rare mutations, newer long-read approaches can detect both mutations and quasi-species of the HIV virus. This approach has enabled detection of rare mutations in HIV. Additionally, by examining patient samples taken at different time points, it is also possible to determine how previously rare mutations became more common.

Because most of resistance mutations crop up in the stretch of HIV genome that houses its protease and reverse transcriptase genes. To detect drug resistance mutations, that 1.4 kilobase region is amplified using PCR and genotyped using the Sanger-based TruGene kit (Siemens), which is now run on Illumina’s MiSeq. Other NGS approaches like Roche/454, and Life Technologies’ Ion PGM also have a high sensitivity for detecting these minor mutations. However, short-read approaches lose the linkage relationship between the mutations although they can detect multiple mutations, but not whether they were all in one strain or housed among a few strains circulating in the patient.
A long-read approach could give both the frequency and phasing information because its read length covers the full length of the PCR product. Reads longer than 10 kilobases are common. Sanger-based approach is unable to detect rare mutations <20% frequency whereas the NGS approaches are sensitive down to about 1%. Knowing which mutations are present and their phasing information can help clinicians decide upon a drug treatment regimen for the patient. Different drugs might be needed to target a virus strain with two mutations as compared to two strains with one mutation each.

**Personalized Treatment of Hepatitis B**

Monitoring of HBV viral load is the most widely used method in assessing liver disease severity, predicting development of cirrhosis and hepatocellular carcinoma, deciding about initiation of antiviral therapy, assessing treatment response as well as early detection of emergence of drug resistance. Clinical outcome and efficacy of antiviral treatment might vary with HBV genotype. The importance of covalently closed circular DNA is also becoming apparent in this regard. Further studies on the development of newer molecular methods for a better management of chronic hepatitis B will minimize morbidity (Chakravarty 2012).

Treatment of chronic hepatitis B with interferon (IFN)-α results in sustained loss of virus replication in as many as 50% of patients. The immunologic disposition of the host and genetic factors of the virus itself are probably the main determinants for an IFN response. There is indeed increasing evidence for the existence of IFN-sensitivity determining regions in the genome of hepatitis viruses. In this setting, known predictive parameters for an IFN response, such as hepatitis B virus (HBV) DNA titers, alanine aminotransferase levels, the degree of liver inflammation, and disease duration, must be considered merely as surrogate markers. Mutations in the HBV gene also influence response to IFN. With the increasing progress in nucleic acid technologies, investigation of viral genetic biomarkers may be integrated in clinical diagnostic routine.

SeqHepB program (Evivar Medical) is a unique viral genomics sequence analysis program that is linked to a HBV genomic database. It is offered as a web-based decision support tool to assist physicians to optimize and individualize the treatment schedule of patients with chronic hepatitis B. The system can be used to identify HBV mutations present in the patient and to determine resistance levels to the various available medications.

Abbott HBV Sequencing test has the CE mark to identify genomic sequences of HBV to guide or monitor therapy and predict or discover drug resistance. It is not intended for screening blood, plasma, or tissue donors for HBV or as a diagnostic test to confirm HBV infection.

**Personalized Treatment of Hepatitis C**

Hepatitis C is the most common blood-borne viral infection in the US, and it is one of the main causes of chronic liver disease. It is estimated that ~4 million persons in the US and 170 million persons world-wide are infected with HCV. The complications of chronic hepatitis C, including cirrhosis and hepatocellular carcinoma, are expected to increase dramatically world-wide over the next 10–20 years. Immunomodulatory/antiviral therapy, employing IFN-α, both alone and in combination with ribavirin, affords the only effective treatment for hepatitis C. Accurate early prediction of response to IFN therapy may decrease or eliminate unnecessary or ineffective treatment, permit greater flexibility in tailoring therapy on an individual basis, and enhance the cost-effectiveness of treatment. Liver biopsy provides valuable information about the baseline severity and subsequent progression of hepatitis C. Severe fibrosis or cirrhosis on the pre-treatment liver biopsy is associated with decreased response rates.

**Responders Versus Non-responders to Treatment for Hepatitis C**

Standard treatment for hepatitis C, weekly injections of PEG-IFN-α and the oral antiviral agent ribavirin can be curative, but only ~40% of patients with the most common subtype of HCV
in the US, genotype 1, will respond to it, and it is not clear who is likely to respond and who is not. The result is that thousands of people spend long months on treatment without any significant long-term benefit. The measurement of viral RNA levels and genotyping may be used to optimize individual patient treatment. Genotype non-1 and a low viral load are the most significant pre-treatment indicators of sustained virological response. The most reliable predictor of a poor virological response is continued seropositivity for viral RNA during therapy. A genetic test that can help predict which patients with hepatitis C will eventually develop cirrhosis, and are in most need of treatment, which looks at variations in seven genes to personalize treatment.

The genomic sequences of independent HCV isolates differ by approximately 10%, and to study the effects of this variation on the response to therapy, amino acid covariance within the full viral coding region of pretherapy HCV sequences were analyzed from participants in the Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C) clinical study (Aurora et al. 2009). Covarying positions were common and linked together into networks that differed by response to therapy. There were 3-fold more hydrophobic amino acid pairs in HCV from non-responding patients, and these hydrophobic interactions were predicted to contribute to failure of therapy by stabilizing viral protein complexes. Using this analysis to detect patterns within the networks, the authors could predict the outcome of therapy with greater than 95% coverage and 100% accuracy, raising the possibility of a prognostic test to reduce therapeutic failures. Furthermore, the hub positions in the networks are attractive antiviral targets to suppress evolution of resistant variants. Finally, covariance network analysis could be applicable to any virus with sufficient genetic variation, including most human RNA viruses.

To predict response of HCV to interferon/ribavirin treatment, analysis has been carried out of serum samples from patients with genotype I who respond to therapy and are cured; from patients with genotype I who do not respond to therapy; and from patients with genotypes 2 or 3 who also respond to therapy and are cured. They broke down the proteins in the serum is broken into into peptides and LC/MS is used to sort the peptides according to molecular weight and charge. Using factor modeling in conjunction with software designed to analyze proteomic data (Rosetta Elucidator), three factors have been discovered representing clusters of proteins or peptides that can predict response to therapy in 9 cases of out 10 cases. Further investigation are needed to determine the protein pathways these clusters are associated with, which may yield information that could lead to new treatment options or more informed treatment decisions using current therapies. These protein signatures will be investigated in a clinical trial.

Ethnicity may play a pivotal role in how patients respond to treatment for HCV. A multicenter, open-label, nonrandomized, prospective study (LATINO Study) has evaluated the effect of Latino ethnic background on the response to treatment with peginterferon alfa-2a (Pegasys®) and ribavirin in patients infected with HCV genotype 1 who had not been treated previously (Rodriguez-Torres et al. 2009). The primary end point was a sustained virologic response. The rate of sustained virologic response was higher among non-Latino whites than among Latinos and absence of HCV RNA in serum was more frequent in non-Latino whites throughout the treatment period. Poor response rate across Hispanics of all nationalities indicates that strategies to improve the sustained virologic response in Latinos are needed.

A sequencing approach to identify DNA variants can predict failure to respond to hepatitis C therapy and help to optimize treatment options for many hepatitis C patients. GWAS to identify genetic factors underlying the lack of viral clearance in most patients revealed that SNPs in the IL28B gene region can predict non-response to treatment. A high-throughput “massively parallel sequencing” approach followed by individual genotyping has been used to identify new, highly sensitive genetic predictors of drug response (Smith et al. 2011). DNA samples from responders or non-responders were pooled, so that many patients could be screened simultaneously and cost-effectively for common mutations. Compared with previous results, the genetic variants identified through this analysis were shown to predict failure to respond with high sensitivity.
and specificity. By predicting which patients are unlikely to respond to the standard treatment, clinicians would be able to make an informed choice about which patients should be offered newly emerging therapies. These results are promising for the personalized management of hepatitis C.

Drug Resistance in Hepatitis C

Genelyzer (Toshiba Hokuto Electronics), an electrochemical DNA chip, has been used to detect resistance to treatment in patients with hepatitis C. Lab21 has patented its use for HCV drug resistance genotyping. This intellectual property covers the analysis of genomic sequence variation in the viral serine protease gene, NS3. This enzyme has an important role in HCV replication and is one of the key areas of attack for the pharmaceutical industry. HCV small molecule drugs include those which inhibit the activity of NS3 (telaprevir and boceprevir). Unfortunately, HCV, similarly to HIV, is likely to select for resistant variants against these drugs, so it will be important to monitor patients for resistance. Lab21 is developing proprietary new assays to monitor the emergence of these genotypic variants.

Challenges for Personalized Management of Hepatitis C

Current knowledge of the genetic and other determinants of HCV-related disease progression and cancer development is still rudimentary. Without a solid understanding of these processes and validated biomarkers, the goal of tailoring treatment to individual patients’ needs will remain elusive. Despite the development of highly effective medications, many treatment challenges persist. Persons infected with HCV genotype 3 and those with liver cirrhosis are least likely to have a response to treatment. Drug resistance can emerge in patients with multiple treatment failures, and there is theoretical concern regarding the spread of multidrug-resistant HCV in such patients, especially among injection-drug users (Liang and Ward 2018).

Personalized Management of COVID-19

A novel coronavirus, designated as 2019-nCoV (COVID-19), emerged in Wuhan, China, in November 2019, but the news were initially suppressed. Although zoonotic in origin, it has a human-to-human transmission and rapidly spread worldwide as the Chinese traveled outside of China. WHO eventually had to declare it as a pandemic. Global case count as August 2020 was >15 million; ±600,000 deaths; ±9 million recovered (https://www.worldometers.info/coronavirus/). Molecular diagnostics and sequencing are important in management of COVID-19 as the infection is asymptomatic in most of the affected persons and mutations occur. Clinical manifestations vary considerably, and severity varies from mild to serious and life threatening. The most critical complications is respiratory failure. Management of COVID-19 is discussed in detail in a special report on antivirals (Jain 2020). Points relevant to personalizing management of COVID-19 are discussed in this chapter.

Molecular Diagnosis of COVID-19

Coronaviruses have genomes encoded by RNA. Therefore, a standard PCR cannot be used to detect the presence of the virus. A real-time reverse transcription PCR (RT-PCR) assay was used to detect viral RNA by targeting a consensus RdRp region of pan COVID-19 (Zhu et al. 2020). Several companies have developed kit tests for the presence of four multiple COVID-19 genes: O, R, N, and E. Mammoth Biosciences wants to expand its efforts beyond CRISPR-based disease detection to create a prototype of a rapid POC molecular test for COVID-19 that can quickly and accurately distinguish the recently-discovered coronavirus strain from all other infectious diseases. A version of the metagenomics platform Explify Respiratory (IDbyDNA) has been upgraded to enable detection of COVID-19 and differentiate it from other coronaviruses. To further characterize the virus, de novo sequences of COVID-19 genome has been carried out from
clinical specimens (bronchoalveolar-lavage fluid) and human airway epithelial cell virus isolates obtained by Illumina and nanopore sequencing.

Although molecular assays for direct detection of the viral genetic material are available for the diagnosis of acute infection, there is lack serological assays suitable to specifically detect SARS-CoV-2 antibodies. Molecular diagnostic tests are not useful in identifying persons who have already recovered from COVID-19, as they will no longer have detectable levels of viral RNA in their body. These recovered patients will, however, have antibodies that fight off the virus circulating in their blood. Serological assays are of critical importance for determining seroprevalence in a population, define previous exposure and identify highly reactive human donors for the generation of convalescent serum for therapy. Sensitive and specific identification of coronavirus SARS-Cov-2 antibody titers will also support screening of health care workers to identify those who are already immune and can be deployed to care for infected patients minimizing the risk of viral spread to colleagues and other patients. However, there is lack of proper test and the value of antibodies in the management of COVID-19 is questionable.

**Genomics of Coronaviruses**

A better understanding of viral pathogenicity and zoonotic transmission is crucial for prediction and prevention of future outbreaks. Use of integrated comparative genomics and machine learning techniques has enabled identification of key genomic features that differentiate SARS-CoV-2 and the viruses behind the two previous deadly coronavirus outbreaks, SARS-CoV and MERS-CoV, from less pathogenic coronaviruses (Gussow et al. 2020). These features include enhancement of the nuclear localization signals in the nucleocapsid protein and distinct inserts in the spike glycoprotein that appear to be associated with high case fatality rate of these coronaviruses as well as the host switch from animals to humans. The identified features could be crucial contributors to coronavirus pathogenicity and possible targets for diagnostics, prognosis, and interventions. The predictions made through this analysis unveil potential critical features in the mechanism of SARS-CoV-2 virulence and its evolutionary history, are amenable to straightforward experimental validation, and could serve as predictors of strains pathogenic to humans.

**Genetic Susceptibility for Severity of COVID-19**

A GWAS in Europe by Host Genetics Consortium, which included de novo genotyping for Covid-19 with respiratory failure, detected a novel susceptibility locus at a chromosome 3p21.31 gene cluster and confirmed a potential involvement of the ABO blood-group system in Covid-19 (Ellinghaus et al. 2020). On chromosome 3p21.31, the peak association signal covered a cluster of six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1), several of which have functions that are potentially relevant to Covid-19. One candidate is SLC6A20, which encodes the sodium–imino acid (proline) transporter 1 and which functionally interacts with ACE-2. It seems reasonable to conclude that the chromosome 3p21.31 locus is involved in Covid-19 susceptibility per se, with a possible enrichment in patients with severe disease. This latter interpretation is supported by the significantly higher frequency of the risk allele among patients who received mechanical ventilation than among those who received supplemental oxygen only as well as by the finding of younger age among patients who were homozygous for the risk allele than among patients who were heterozygous or homozygous for the nonrisk allele.

The ABO locus holds considerable risk for population stratification, which is increased by the inclusion of randomly selected blood donors in the current study (for which there is an inherent risk of blood group O enrichment).

In young male patients with severe COVID-19, rare loss-of-function variants of X-chromosomal gene TLR7 were identified by whole exome sequencing, which were associated with impaired type I and II interferon responses rendering them susceptible to the virus infection (van de Made et al. 2020).

Although apolipoprotein E4 (apoE4) apoE has been classically associated with lipoprotein metab-
olism and atherosclerosis, it is also associated with the risk of susceptibility to viral infections. ApoE4 genotype may predict the propensity to manifest rapid and severe illness with COVID-19. It is also noteworthy that apoE is expressed by many cell types in the lung, including macrophages and both Types I and II alveolar epithelial cells; while the functional receptor for SARS-CoV-2, angiotensin-converting enzyme 2, is highly expressed on Type II alveolar cells. Moreover, the local pulmonary apoE concentration acts as a danger signal in asthmatics, which activates the inflammasome and subsequently interleukin-1β production by macrophages. Therefore, it is possible that having one or two copies of apoE4 predisposes one to be at high risk to progress to severe illness from SARS-CoV-2, by virtue of a sequence of robust innate immune response, followed by cytokine storm and resulting ARDS. Furthermore, apoE polymorphism may explain in part why African Americans appear to be disproportionally affected with severe illness from COVID-19, in addition to other well-known socioeconomic inequalities and risk factors. The apoE genotype is easily obtained by buccal swab analysis or blood test, and investigators should determine if having a copy of apoE4 does indeed predict more severe COVID-19 and death. If so, this group could be targeted more aggressively from the outset of the disease (Goldstein et al. 2020).

Strategies for Developing Therapies for COVID-19

The laborious classic pathway for the discovery and approval of new drugs is less well suited to the present pandemic of COVID-19. Repurposing existing drugs offers a potentially rapid method for deployment because the safety profiles are known. A preliminary report of a supercomputer-driven ensemble docking study of a repurposing compound database to the viral S protein with 8000 compounds ranked according to the calculated binding affinity to the receptor-binding domain of the S protein (Smith and Smith 2020). Top-ranked compounds from the original S-protein virtual screen are being tested for activity against the live virus. The results will guide future calculations of targets.

However, in the surreal, accelerated world of Covid-19 research, advances are quickly out of date. Many new experimental 3D structures of the S protein and other viral targets are being reported in quick succession, a process that requires the simulations and docking to be refined and repeated. Artificial intelligence is being used to predict drug binding. Different types of experimental laboratory screening programs have been set up all over the world and are ramping up. Meanwhile, for several SARS-CoV-2 proteins, the virtual high-throughput screening and ensemble docking pipeline is in full production mode, both on supercomputers and with the use of vast cloud-computing resources. None of this guarantees success within any given time frame, but a combination of rationality, scientific insight, and ingenuity with the most powerful tools available will give us our best shot (Parks and Smith 2020).

Antivirals for COVID-19

There is no approved drugs or vaccines for treatment of COVID-19. Some of the drugs under investigation are not direct antivirals but reduce the complications of COVID-19 such as pneumonia. Several antiviral drugs approved for other viral diseases have proved useful in the management of COVID-19 and are being repositioned to undergo clinical trials for COVID-19. By August 2020, there were >300 legitimate drug and vaccine COVID-19 candidates listed: https://www.genengnews.com/covid-19-candidates/covid-19-drug-and-vaccine-tracker/. The two most publicized repurposed drugs being tested in clinical trials for the current COVID-19 pandemic are hydroxychloroquine and remdesivir.

In addition to the use of drugs that were discovered for other viral diseases, considerable efforts are being made to develop active substances against SARS-CoV-2. The structural analysis of functional proteins of the virus is very helpful for this goal. The function of a protein is closely related to its 3D architecture, which could be helpful for identification of specific targets for active substances. A special protein, the viral main protease (Mpro, 3CLpro), is responsible for the reproduction of the viruses, because of its essential role in processing the polyproteins that are translated.
from the viral RNA. The X-ray structures of the unliganded SARS-CoV-2 Mpro and its complex with an α-ketoamide inhibitor has been reported (Zhang et al. 2020). This was derived from a previously designed inhibitor but with the P3-P2 amide bond incorporated into a pyridone ring to enhance the half-life of the compound in plasma. Based on the structure, the authors developed the lead compound SARS-CoV-2 Mpro. Pharmacokinetic characterization of the optimized inhibitor reveals a pronounced lung tropism and suitability for administration by the inhalation.

Cell/Gene Therapy for COVID-19

Safety and effectiveness of intravenous allogeneic cardiosphere-derived cells (CDCs), formulated as CAP-1002, has been studied in critically ill patients with confirmed COVID-19 (Singh et al. 2020). CDCs display immunomodulatory and antiinflammatory effects in severe COVID-19 with cytokine storm.

RNA-targeting CRISPR systems can be effective in targeting RNA viruses such as the coronaviruses or influenza viruses. To improve the targeting of an RNA-targeting CRISPR system, the enzyme Cas13 is used to complex with guide RNA, which binds to complementary mRNA. The better the match between the guide RNA and the mRNA, the more effective the Cas13’s gene silencing action will be. A platform for conducting massively parallel genetic screens at the RNA level in human cells has been engineered and the screening technology can be used to understand many aspects of RNA regulation and to identify the function of ncRNAs (Wessels et al. 2020). By targeting thousands of different sites in human RNA transcripts, the researchers developed a machine learning-based predictive model to expedite identification of the most effective Cas13 guide RNAs.

Personalized Approach to Passive Antibody Therapy for COVID-19

A study from New York has shown that data show that a large proportion of convalescent plasma samples have modest antibody levels and that commercially available tests have varying degrees of accuracy in predicting neutralizing activity, whereas other tests are capable of accurately measuring levels of antibodies that strongly correlate with neutralization assays (Luchsinger et al. 2020). These findings imply that SARS-CoV-2 convalescent plasma donors have a wide range of antibody concentrations. More data needs to be collected to understand why recovered patients have such a wide range in antibody levels, and how that could affect a person’s ability to fight off future infections with the virus. The findings imply, for example, that there may be different ways of fighting SARS-CoV-2 infection. As all subjects reported in the study recovered from their infections, the immune systems of some may rely heavily on antibodies, while others turn to different types of cells to fend off the virus. The results make a strong case for physicians not to test just for antibody levels, but to learn what those levels might mean for each patient’s ability to fight further infection. This would enable a personalized approach to passive antibody therapy for COVID-19.

Personalized Vaccines for COVID-19

No specific vaccine is yet available for protection from COVID-19. As the sequence of SARS-CoV-2 is available, efforts are being made to develop a vaccine. Approximately 100 vaccines and immunological approaches were in development for COVID-19 as of August 2020.

Vaccines based on recombinant DNA platforms combine DNA sequence encoding the antigen with DNA of the baculovirus expression platform for rapidly producing large quantities of the coronavirus antigen to stimulate the immune system to protect against the virus. Such vaccines are slow to produce but has demonstrated partial protection as assessed in animal challenge models.

An mRNA printer capable of producing thousands of doses of mRNA vaccine encapsulated in lipid nanoparticles. Viral targets for its mRNA vaccine are based on the past successful approach to development of a MERS vaccine showed that the technology did induce antibodies against the MERS corona virus. In a phase I
study on healthy volunteers, the mRNA-1273 vaccine induced anti–SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified (Jackson et al. 2020). The investigators also tested the antibodies taken from study participants against actual samples of SARS-CoV-2 and found their ability to neutralize virus was at least equivalent to that found in persons who had recovered from infection. How long the vaccine-induced immune response lasts to protect against COVID-19 is not known; the 45 participants in this study will be monitored for a year to find out. Moderna is now starting a placebo-controlled phase II study of the vaccine, which will include 300 persons, and continue to evaluate safety and efficacy of the vaccine as well as determine the right dose for the final phase of testing by the end of 2020. The FDA has also already authorized the phase III trial on 30,000 persons, which will also compare the efficacy of the vaccine against a placebo.

Anti-COVID-19 vaccines clearly face some big challenges, both scientific and logistical. One of the biggest challenges facing researchers developing a COVID-19 vaccine is understanding how the immune system interacts not only with the pathogen but with the vaccine itself as both need to be considered for a safe and effective vaccine. Vaccine candidates for diseases such as dengue, RSV, and SARS have shown a paradoxical phenomenon; those who received the vaccine and were later exposed to the virus developed more severe disease than those who had not been vaccinated. Immune enhancement, also referred to as vaccine enhancement, is a concern. Efforts are under way to define what exactly this enhancement means, and what the relevant issues are for a COVID-19 vaccine, and what to do with that information (Peeples 2020).

Although disease enhancement by antibodies has been described for corona and other viruses, nobody can predict whether such antibodies induced by the vaccine will not be harmful, especially after reinfection with a different strain. To address this problem, a concept for personalized vaccine with companion diagnostic has been described with the following steps (Lisziewicz and Lori 2020):

- Design of vaccines that could induce memory T cell responses, in the absence of antibodies, to kill newly infected cells.
- Preclinical testing of such personalized vaccines is performed in silico without animal experiments since epitopes predicted to bind to three HLA class I molecules of a subject activate cytotoxic T cell response with >80% probability.
- Bioinformatic tools can be used to select immunogenic vaccine peptides from the coronavirus replicase protein and estimate the immune response rate in an HLA-genotyped population.
- Employing accessible platform technologies, a set of personalized vaccines could be co-developed with an HLA-genotype based companion diagnostic to identify the vaccine that most likely induces responses in the subject.
- The goal of personalized vaccination is to convert the deadly COVID-19 into asymptomatic disease and to avoid the potential risk of disease enhancement.

**Personalized Management of Tuberculosis**

Tuberculosis (TB) is a global pandemic that threatens to overwhelm healthcare budgets in many developing countries. It is estimated that at least 8 million people develop active TB annually, of whom 2 million die. It has been the cause of a global health emergency for over 10 years owing to factors such as social stigma, patient compliance, and lack of investment in a thorough TB control program. Despite the availability of adequate effective treatment, many patients default on treatment, experience adverse side effects from antibiotics or fail to respond rapidly and recover. These factors have resulted in the worrying emergence of drug resistance, leading to multi-drug resistant (MDR) and extensively drug resistant (XDR) strains of TB becoming prevalent. This is particularly a problem in the developing world, where most of patients with TB also have HIV, making effective eradication extremely difficult.
Isoniazid, one of the most important first-line tuberculosis drugs, is acetylated in the liver to a variable degree in different individuals giving rise to fast, intermediate and slow acetylator phenotypes. Different genetic mutations may play a role in determining how a patient will respond to the commonly used TB medication isoniazid. Acetylation status of individuals plays an important contributory role in the tuberculosis pandemic. It is important to study the acetylation alleles, and to understand isoniazid metabolism and how it could affect patient compliance, isoniazid toxicity, and the emergence of drug-resistant strains of mycobacteria. These phenotypes have been linked to different genetic variants, primarily present in the NAT2 gene (see Chap. 3). The standard drug dose currently administered to patients, regardless of their acetylator status, may not be appropriate for certain people. Individualization of isoniazid therapy may help to prevent adverse drug reactions experienced by a small percentage of patients thought to be ‘slow-acetylators’ of the drug. Conversely fast-acetylators may not be receiving adequate amounts of the drug to combat TB successfully, therefore increasing the likelihood of a relapse and development of drug resistance. Confirmation of the genetics of isoniazid metabolism by a simple test to determine acetylator status would be desirable and this should be available at the same laboratories that currently perform diagnostics for TB.

**Personalized Management of Fungal Infections**

Treatment or prophylaxis of invasive fungal infection in recipients of hemopoietic stem cell transplant (HSCT) may require management of coexistent malnutrition, organ dysfunction and graft versus host disease, all of which create added potential for inter- and intra-patient variations in drug metabolism as well as drug interactions. Polymorphism is common in genes encoding pathway components of antifungal drug metabolism such as enzymes (cytochrome P450 (CYP450), glutathione S-transferase, N-acetyltransferase and uridine 5'‐diphosphoglucuronosyltransferase), uptake transporters (organic cationic transporter, novel organic cationic transporter, organic anion transporter protein, organic anion transport, and peptide transporter) and efflux transporters (breast cancer resistance protein, bile salt export pump, multidrug and toxin extrusion type transporter, multidrug resistance protein, permeability glycoprotein, and urate transporter). Specific polymorphisms may be generalized throughout a population or largely confined to ethnic groups. CYP450 enzymes, especially 2C9 and 2C19, exhibit extensive polymorphism and are central to the metabolism of azole antifungals and their interactions with other drugs including calcineurin inhibitors, cytotoxics and benzodiazepines. Polymorphism may ultimately affect drug efficacy: CYP2C19 variation leads to a 5-fold variation in voriconazole levels between individuals. In the future, routine provision of pharmacogenomic data for new drugs together with accumulating knowledge about established agents will challenge physicians to assimilate and apply that information in drug prescribing (Ashbee and Gilleece 2011).

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