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Innovations in health and demographic surveillance systems to establish the causal impacts of HIV policies

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Abstract

Purpose of Review—Health and Demographic Surveillance Systems (HDSS), in conjunction with HIV treatment cohorts, have made important contributions to our understanding of the impact of HIV treatment and treatment-related interventions in sub-Saharan Africa. The purpose of this review is to describe and discuss innovations in data collection and data linkage that will create new opportunities to establish the impacts of HIV treatment, as well as policies affecting the treatment cascade, on population health, economic and social outcomes.

Recent Findings—Novel approaches to routine collection of (i) biomarkers, (ii) behavioural data, (iii) spatial data, (iv) social network information, (v) migration events and (vi) mobile phone records can significantly strengthen the potential of HDSS to generate exposure and outcome data for causal analysis of HIV treatment impact and policies affecting the HIV treatment cascade. Additionally, by linking HDSS data to health service administration, education, and welfare service records, researchers can substantial broaden opportunities to establish how HIV treatment affects health and economic outcomes, when delivered through public-sector health systems and at scale.

Summary—As the HIV treatment scale-up in sub-Saharan Africa enters its second decade, it is becoming increasingly important to understand the long-term causal impacts of large-scale HIV treatment and related policies on broader population health outcomes, such as non-communicable diseases, as well as on economic and social outcomes, such as family welfare and children's educational attainment. By collecting novel data and linking existing data to public-sector records, HDSS can create near-unique opportunities to contribute to this research agenda.

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Conflicts of interest

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Keywords

Health and Demographic Surveillance; treatment Cohorts; data collection; data linkage; biomeasures

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Introduction

Together with HIV treatment cohorts, Health and Demographic Surveillance Systems (HDSS) have made important contributions to our understanding of the HIV epidemic and the impact of interventions against it (1–3). This article discusses innovations in data collection in HDSS to create novel opportunities to generate data on the HIV treatment cascade and to establish the causal impacts of policies and interventions intended to improve progression through the cascade.

Health and Demographic Surveillance (Dynamic Longitudinal Population-based Cohorts)

HDSS (4–6) follow entire geographically defined populations through regular household surveys to establish a longitudinal database of individuals and social units in surveillance areas. These population-based and open cohorts allow the monitoring of population mortality and life expectancy over time (7, 8), and consequently the impact of interventions such as the introduction of antiretroviral therapy (ART) on mortality and life expectancy (3, 9), as well as on a wide range of economic, social and behavioural outcomes. Typically, in HDSS verbal autopsies (10–12) are used to determine cause-specific mortality including HIV-related mortality (13–15). Some HDSS regularly collect HIV serostatus from the survey population (16, 17) providing further insight into the epidemiology of HIV, such as the direct measurement of HIV incidence (18), the spatial distribution of HIV risk (19), and treatment uptake among HIV-infected individuals from a population perspective. HDSS data has previously been used to show the full population impacts of ART on life expectancy (3) and HIV transmission (2), as well as the causal effects of ART on employment (20), education, contraception (21), and health care seeking (22). The ability to study causal impacts of ART on outcome variables collected in HDSS is gained through data linkage between the population-based HDSS data and clinical HIV treatment exposure. HDSS data can be linked to two broad categories of clinical cohorts: health systems cohorts of patients in routine care and treatment cohorts specifically designed for research.

Health System Data Collection

Of the approximately 12 million people globally receiving ART more than 8 million live in Sub-Saharan Africa (SSA) (23). However, health services in SSA are often overburdened and high-quality medical records are not typically available. Nevertheless, as the region with the highest HIV burden, it is in SSA where the biggest need exists for accurate data on the treatment cascade. The Africa Centre for Health and Population Studies (24) and other HDSS in SSA have pioneered linkage of routine HIV treatment health systems data to population-based data at the level of the individual. Typically, these initiatives have included investments in improved public-sector data collection systems and extraction of data from patient records. Electronic record systems can play an important role in facilitating such data linkage (25–31). While potentially limited in content, when widely implemented and of

sufficient quality, electronic medical records capturing the care of patients in routine HIV care have the benefit of providing access to much larger patient numbers than can be managed through treatment cohorts that are specifically funded and managed for research purposes. In South Africa, the country with the highest number of individuals on ART, approximately two-thirds of the nationwide close to 4000 public-sector ART clinics have fully implemented an electronic patient register (32). Rolling out electronic record systems more widely across SSA could benefit both clinical care, and our ability to understand how ART is affecting outcomes in routine care and at the population level.

Specific treatment Cohorts

In addition to “health systems” treatment cohorts, there are essentially two types of treatment cohort designs commonly adopted in HIV research. First, there is the traditional fixed cohort (such as the Multicenter AIDS Cohort Study or MACS (33)), in which patients are specifically recruited and follow a defined visit structure, such as six or twelve monthly, with standardised assessments made on all patients at each visit. Second, and much more common, are observational cohorts (such as EuroSIDA (34) and the Australian HIV Observational Database or AHOD (35)), in which patients are passively followed, and data is largely collected through routine medical care visits. Fixed cohorts have the advantage of standardised measurements on all patients at a fixed visit structure, making statistical analysis and inferences easier. Observational cohorts, often based on electronic medical records, are much cheaper and easier to maintain, and arguably more accurately reflect true patient care and outcomes. Larger multi-cohort collaborations have also been successfully established. The Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study is a multi-cohort collaboration across Europe, America and Australia (36), which assesses the effect of ART on long-term clinical outcomes, such as cardiovascular disease, cancer, and liver and kidney failure.

The relationship between “health systems” cohorts and specific treatment cohorts maintained primarily for research purposes is fluid, because specific treatment cohorts are often build on health systems core data. For instance in the International epidemiological Database to Evaluate AIDS (IeDEA) data from many different sites, including public-sector HIV treatment programmes, are pooled and jointly curated (37, 38), allowing research across time and different geographical regions.

Observational cohort data have been, and will remain, useful in monitoring how changes in treatment and management guidelines actually result in changes in treatment of HIV-positive patients. For example, treatment guidelines have rapidly changed over the last few years from starting ART at CD4<200 cells/μL, to CD4<350 cells/μL, to CD4<500 cells/μL, and more recently in some countries to no CD4 threshold in key populations. The IeDEA network was able to assess how CD4 count at initiation of ART has actually changed in response to these changes in guidelines, showing that while there have been some trends to earlier ART, treatment initiation still mostly occurs relatively late – at median CD4 counts of less than 150 cells/μL in low and middle income countries (39).

In this paper, we focus on innovations in data collection and data linkage in those HDSS cohorts that have been linked to HIV treatment data available in the routine health system

and in specific treatment cohorts. A number of approaches to establish causal relationships have recently been adapted for use with this type of longitudinal data and are increasingly applied to answer causal questions regarding the HIV treatment cascade (40). These approaches include fixed-effects analyses (41), marginal structural models (42), instrumental variable analyses, and regression discontinuity analysis (43–45). These approaches are discussed in another paper in this issue (Bor et al.). The objective of this paper is to introduce novel data opportunities to provide better exposure and outcome measures for causal evaluation of the impacts of HIV treatment as well as health policies and interventions to improve progression through the HIV treatment cascade.

Innovations

To establish causal relationships related to the HIV treatment cascade, the following are needed: (1) data on cascade exposures and outcomes, (2) the ability to link these exposure and outcome data within relevant units of observation, and (3) data structures and approaches sufficient for causal inference. Here, we focus on innovations in building the data infrastructure to enable causal analyses of the HIV treatment cascade using health systems and routine treatment cohort data; Bor et al.'s article in this issue focuses on novel analytical approaches to establish causality in quasi-experimental studies of interventions to improve the HIV treatment cascade.

Novel Data Collection

Additional Biomeasures

To establish the causal impacts of HIV treatment, policies and interventions to improve the HIV treatment cascade at the population level a range of biomarkers of disease will be useful (46). For instance, as a result of the ART scale-up in SSA, a new population is emerging: older adults in SSA who have lived with HIV for more than a decade and have received ART for many years (47). After HIV, cardiovascular disease (CVD) and diabetes are already the most common cause of death and premature mortality in many countries in SSA, such as South Africa (48, 49), and it is expected that survival of HIV-positive populations into old age due to ART will reveal cardiometabolic disease burdens previously "hidden" by high HIV mortality (47, 50). However, the patterns and extent of the expected epidemiological transition from HIV/TB to cardiovascular disease and diabetes due to the ART scale-up in SSA remains largely unknown. Adding detailed biomarker data to existing HDSS on markers of cardiovascular disease and risk (e.g., lipid profiles, creatinine, and markers of long-term blood sugar, such as HbA1c), will create opportunities to establish causal impact of ART on cardiometabolic disease in relevant populations. The range of biological measures available through non-invasive (e.g., hair samples) or minimally invasive (e.g., dried blood spots) techniques are increasing. Table 1 provides a non-exhaustive list of biomeasures currently available on dried blood spots. Biomarkers particularly relevant to population-based HIV research that can be measured using dried blood spots include HIV viral load and the serum concentration of antiretroviral drugs, but also measures of cardiovascular risk (e.g., triglycerides) and diabetes-related measures (e.g., glycated hemoglobin A1c (HbA1c)), which may be affected by antiretroviral therapy. For many important indicators, however, venous blood samples will have to be collected at the

population level. Currently, few HDSS routinely collect venous blood, but such data collection is theoretically possible and is likely to be increasingly employed. One approach is to introduce venous blood data collection during the standard HDSS household visits and then, given consent, to send a specialized phlebotomy team to a household for venous blood-letting.

Behavioural Data Collection

Measuring health behaviours – including behaviours relevant to the HIV treatment cascade, such as medication adherence – is complicated by the difficulty of validating self-reported behavioural data and the potential for misreporting due to social desirability (148), especially if continued ART provision is believed to be linked to self-reports of behaviours (149). Biases are likely to be exacerbated by verbal responses, since such answers are then known to the interviewer and others within earshot. Self-interview methods (notably computer-assisted self-interviews [CASI]) have been shown to increase reporting of socially undesirable behaviours, particularly sexual behaviour (150, 151). Self-report of HIV diagnosis, engagement in care and ART receipt may thus also be improved by CASI methods, as has been previously proposed (152). The addition of pictorial representations of medications may further improve validity (153). Substantive use of CASI methods in HDSS work has historically been limited by concerns regarding reading and computer literacy. However, increasing availability of audio-CASI methods – where respondents use headphones to listen to questions and response options – and rising market penetration of mobile- and now smart-phones, is making the use of CASI increasingly acceptable and practical.

Community Exposure and Spatial Data

There is increasing recognition of the need to develop explanations of outcomes that incorporate individual and community-level factors and move away from an individual-centred approach to understanding causal relationships (154–156). Many HDSS sites now routinely collect spatial data as part of the ongoing surveillance activities. This spatial data can be used to create community-level exposure variables to use in causal analyses. For example, at our HDSS site in rural KwaZulu-Natal we have shown that, after controlling for multiple variables associated with uptake of ART, an individual living 4.78km from a clinic was 50% less likely to be on ART relative to someone living next to a clinic (157). We have recently demonstrated the causal impact of community coverage of ART in reducing an individual's risk of HIV acquisition. Holding other key HIV risk factors constant, individual HIV acquisition risk declined significantly with increasing ART coverage in the surrounding local community. For example, an HIV-uninfected individual living in a community with high ART coverage (30 to 40% of all HIV-infected individuals on ART) was 38% less likely to acquire HIV than someone living in a community where ART coverage was low (<10% of all HIV-infected individuals on ART) (2). Adding geographical location data to existing HDSS datasets already including the location of people's homes, will improve the assessment of access and exposure to public services (such as primary care clinics, HIV testing and counselling facilities, government grant distribution infrastructure, and schools) that can affect progression through the HIV treatment cascade. In using distance to a particular facility, however, it is important to keep in mind that the standard approach to

protect individuals' privacy when working with geo-location data – i.e., adding a random spatial errors to true location coordinates or "scrambling" – will lead to systematic overestimation of the distance between people's homes and other places, such as facilities where services can be accessed (158).

Network Exposure and Contact Data

Accurate measurement of each step of the treatment cascade is crucial to predicting future population health, and thus required resources. Standard models of resource use implicitly assume that non-testing, non-use of care and non-adherence are random within the population. However, in practice individuals tend to act similarly to their contacts (e.g. friends, family, work colleagues) (159). This homophily has important implications for epidemic control. Typically, homophily implies that greater intervention efforts are required than were behaviour randomly distributed through the population. This requirement arises because interventions evenly spread throughout the population can either entirely miss some high-risk subgroups or have insufficient impact to control transmission from members of these sub-groups. In both cases, the high-risk subgroups will continue to generate new infections. Behaviour patterns can be elicited in surveys either by asking respondents to report on their contacts' behaviour (egocentric networks), or by gathering contacts' identifiers and thus building an overall picture (sociocentric networks) (160). Careful modelling that takes account of network structures can then be used to estimate how the HIV epidemic is likely to progress (161, 162), and how it is likely to respond to interventions (163–165), in light of these contact patterns.

Tracking migration events and use of mobile phone data

In another article in this issue we review recent work done on the HIV treatment cascade in migrants and mobile populations.(166) Realizing the full treatment and preventative benefits of the UNAIDS 90-90-90 strategy will require reaching all vulnerable sub-populations of which migrants are a particularly important group. One area that HDSS sites could contribute significantly is the followup of HIV-infected patients who have disengaged from the health-care system. Mobile individuals are at a significantly higher risk of being lost to follow up (LTFU) within ART programs. (167–170) However, typically only a proportion of those declared to be LTFU actually disengage from care. (171) The ability to track people as they move from one area to another area is essential to assure their continued HIV care, and to generate valid estimates of each step of the treatment cascade and as well as objective LTFU rates. (171) Standard HDSS sites typically do not measure outcomes on individuals who are no longer resident in their respective study areas. Some HDSS sites such as the Agincourt and the Africa Centre HDSS in South Africa continue to collect information on household members who are no longer predominantly resident in the study area but who may continue to return intermittently (172–174). While such information can yield valuable information, it does not go far enough. It has recently been estimated that the worldwide penetration rate of cellular phones will soon be 97% with more than 7 billion subscriptions. (175) HDSS sites could harness mobile phone technology to track individuals in time and space, collect information via electronic questionnaires and facilitate the interaction with health care providers. Rather than assuming a single neighbourhood influence, mobile phone technology offers the opportunity to measure the dynamic context surrounding an individual

– that is the combination of physical locations the individual occupies in their existence that places him or her at additional risk of adverse health outcomes. The use of mobile health (mHealth) technology to improve HIV treatment outcomes is comprehensively reviewed in this issue(166) and elsewhere. (176)

Data Linkage

The linkage of routine administrative records (177), including medical records, to surveillance populations offers an important opportunity to study the impact of public health intervention on the HIV treatment cascade. Effective record linkage is greatly assisted by broadly-used unique individual identifiers. Most developing countries lack population registration systems that facilitate the availability of such identifiers, and thus linking datasets requires probabilistic linkage techniques (178). HDSSs are in a strong position to collaborate with local authorities to improve the availability of government identity documents in the surveillance population (179), or to issue identity cards to facilitate identification. Linkage to surveillance populations need not be restricted to health service records: linkage to other administrative records could offer additional information or verify self-reported information that would increase our understanding of reasons for failures in the treatment cascade or to evaluate interventions to improve HIV care:

1. *Health Service Administrative Data*. Extracts from routine administrative systems, such as human resources, financial and logistics systems can be used to determine the impact of personnel movement and staffing levels in ART programmes on health system outcomes. Access to financial and logistics data will allow for more detailed and ongoing activity costing at service delivery level to better quantify the costs associated with specific interventions.

2. *Education Records*. Linkage to school records will provide more detailed information on educational attainment and school absenteeism to broaden our understanding of the impact of interventions and determinants of intervention success.

3. *Welfare Service Records*. In countries where individual social support services (e.g. state-sponsored old age pensions, health insurance, child support and disability grants) exist, linkage will allow us to study how these programmes mitigate the impact of HIV-related mortality or morbidity, and affect access to and retention in HIV care.

4. *Other data sources*. There are a wide variety of other data sources that could usefully be linked to the population-based data, but where data access barriers or identity disclosure risks currently limit the potential of these data sources. For example access to mobile phone call meta-data could improve our understanding of the role of human mobility in the observation of small scale geographic variability in HIV acquisition risk or on the retention in care of patients.

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Conclusions

Health and demographic surveillance systems are excellent scientific infrastructures for establishing population impacts of health interventions, in particular those that affect large proportions of the population, such as HIV treatment in high HIV prevalence settings. Innovations in data collection and data linkage in these surveillance systems can substantially enhance the scientific opportunities to establish the impacts of HIV treatment on outcomes, and the effects of health policies and intervention on the HIV treatment cascade. In particular, recent innovations in *data collection* can be harnessed to expand and improve the assessment of biomarkers, behavioural data, community exposures and spatial data, and social network and contact data. In particular, biomarkers of high relevance to population-based HIV research, such as HIV viral load and markers for cardiovascular risk, can now be reliably measured using the minimally invasive dried blood spots. Longitudinal and geographically linked data using geographic information systems, monitoring of migration and mobile phone tracking allow individuals to be accurately located in time and place. These data can provide novel and rich data analytical opportunities for the study of HIV treatment impacts and interventions to improve the treatment cascade, when they are nested within the overall population-based cohort data infrastructure that HDSS provide. Additionally, through *data linkage*, routine medical records, and education and welfare service records can be used to provide novel data on exposures and outcomes that are relevant for studies of the treatment cascade, such as the effects of education on cascade progression.

In order to gain the research opportunities on ART impacts and cascade progression that can become available through innovations in HDSS data collection and data linkages, researchers will need to build scientific infrastructure and political relationships. Particularly important components of the scientific infrastructure include data management specialists, computing environments, and laboratory capacity. Building close relationships with both policy makers and programme managers is crucial not only to gain access to routine programme and administrative data, but also to understand how policies intervene in the data generation processes. These investments in research capacity and relationships with policy-makers aiming to enhance HDSS data are likely to generate large returns, increasing the evidence that is needed to ensure that the ART scale-up can be sustained over the coming decades and continues to improve population health outcomes.

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Key points

- This article provides a summary of the role and research potential of health and demographic surveillance systems in advancing knowledge and informing health policies to improve the HIV treatment cascade and ART population impacts.
- Particular innovations include expanded and improved collection of biomarkers, behavioural data, community exposures and spatial data, and social network and contact data, which will generate novel exposures and outcomes for causal analyses of the HIV treatment cascade.
- Data innovations further include data linkage of HDSS data to routine medical records, and education and welfare service records.

Table 1

Biomarkers that can be measured using dried blood spots

Viral infections		
Measure	**Use**	**Method**
HIV (51–53)	Measuring HIV viral load	Nested PCR, RNA assays, RT-PCR
HIV (54)	HIV serotyping	ELISA
Hepatitis C virus (52, 55)	Monitoring hepatitis C infection	RT-PCR
Antibodies to hepatitis C virus (56, 57)	Detecting hepatitis C infection	ELISA
Human papillomaviruses, hepatitis C virus, and John Cunningham polyomavirus (58)	Detecting infections with the human papilloma virus, hepatitis C virus, or the John Cunningham virus	ELISA multiplex
Hepatitis B virus (59)	Monitoring hepatitis B infection	RT-PCR
Antibodies against hepatitis B (60, 61)	Detecting hepatitis B infection	ELISA
Maternal antibody to hepatitis B (62)	Detecting hepatitis B infection	CORECELL
Antibodies against hepatitis A virus (63, 64)	Detecting hepatitis A infection	ELISA
Measles and rubella immunoglobulin M and G (65)	Detection of measles and rubella infection	ELISA
Rubella virus (66)	Detection of congenital rubella	EIA
Dengue virus (67)	Diagnosis of dengue virus infection	EIA
Epstein-Barr virus (68)	Detection of Epstein-Barr virus infection	ELISA
Human herpes virus type 6 (69, 70)	Differentiation of active from inherited herpes virus type 6 infection	Real-time PCR
Cytomegalovirus (71, 72)	Detection of human congenital cytomegalovirus infection	Real-time PCR
Antibody against human T-lymphotropic virus 1 and 2 (73)	Detection of human T-lymphotropic virus infection	ELISA
Bacterial infections		
Measure	**Use**	**Method**
Antibody against syphilis (74)	Diagnosis of syphilis	ELISA
Antibody against *Treponema (75)*	Diagnosis of syphilis	Indirect hemagglutination test
Antibodies against *Clostridium tetani* (76)	Screening of tetanus and diphtheria toxins	ELISA
Antibodies against *Brucella* (77)	Diagnosis of human brucellosis	ELISA
Antibodies against *Coxiella burnetii, Bartonella quintana*, and *Rickettsia conorii* (78)	Diagnosis of Rickettsial diseases	Immuno-fluorescence
Antibodies against *Pseudomonas aeruginosa* (79)	Detection of *Pseudomonas aeruginosa* infection, mostly in patients with cystic fibrosis	ELISA
Helicobacter pylori (58)	Detection of *Helicobacter pylori* infection	ELISA multiplex
Parasitic infections		
Measure	**Use**	**Method**
Anti-malarial antibodies (80)	Diagnosis of malaria	ELISA
Antibody against *Trichomonas vaginalis* (81)	Seroepidemiology of *Trichomonas vaginalis*	ELISA
Antibody against *Trypanosoma cruzi* (82)	Diagnosis of *Trypanosoma cruzi* infections	ELISA
Antibodies against cysticercus (83)	Detection of anti-cysticercus antibodies	ELISA
Toxoplasma gondii-specific immunoglobulin M and A (84)	Screening for congenital toxoplasmosis	DELFIA

Cardiovascular risk

Measure	Use	Method
Apoliproteins B (85)	Diagnosis and monitoring of hypercholesterolemia	ELISA
Triglycerides (86)	Diagnosis and monitoring of hypertriglyceridemia	Enzymatic method
C-reactive protein (87–89)	Assessment of cardiovascular risk	ELISA
Cystatin-C (89)	Assessment of kidney function and cardiovascular risk	ELISA

Drug concentration

Measure	Use	Method
HIV antiretroviral drugs (NVP, SQV, ATV, APV, DRV, RTV, LPV, EFV, ETV) (90, 91)	Monitoring of drug levels and adherence in HIV patients	LC-MS
Quinine, mefloquine, sulfadoxine, pyrimethamine, lumefantrine, chloroquine (92, 93)	Monitoring of drug levels and adherence in malaria patients	LC/MS
Cocaine metabolite (benzoylecgonine) (94)	Assessing neonates' exposure to cocaine	RIA
Theophylline (95)	Monitoring of drug levels and adherence in obstructive respiratory disease patients	Fluorescence polarization immunoassay

Cancer screening

Measure	Use	Method
Prostate specific antigen (96)	Prostate cancer screening	Chemiluminescent immunoassay
Immunoglobulin G and A (68)	Nasopharyngeal carcinoma screening	ELISA

Hormonal state and diseases

Measure	Use	Method
Glycated hemoglobin A1c (HbA1c) (89, 97, 98)	Diagnosis and monitoring of diabetes	Turbidimetric immunoassay
Insulin (99)	Diagnosis of hyperglycemia/hyper-insulinemia	RIA
Blood glucose (100)	Monitoring of diabetic patients	Enzymic methods
Thyroglobulin (101)	Assessing thyroid status	DELFIA
Thyroxine-binding globulin (102)	Diagnosis of neonatal hypothyroidism	Column chromatography
Thyroid antibody (103)	Detection of autoimmune thyroid disorders	ELISA
Thyroxin (T4) and Thyroid stimulating hormone (104)	Diagnosis of congenital hypothyroidism	LC-MS/MS
Free thyroxine (105)	Assessment of thyroid status	Chemiluminescence
Luteinizing hormone and follicle-stimulating hormone (106)	Variety of uses	Immuno-fluorometric assays
Somatedin-C (107)	Screening test for growth hormone deficiency	RIA
Insulin-like growth factor (108)	Evaluation of growth hormone status	ELISA, RIA

Genetic diseases

Measure	Use	Method
Thyroid-stimulating hormone immunoreactive trypsin, creatine kinase MM isoenzyme (109)	Diagnosis of congenital hypothyroidism, congenital adrenal hyperplasia, and muscular dystrophy	Fluorometric immunoassay
α_1-antitrypsin (110)	Diagnosis of α_1-antitrypsin deficiency	Immune nephelometry
α-Fetoprotein (111)	Assessing fetal risk of open neural tube defects and Down syndrome	ELISA

Biotinidase (112)	Diagnosis of biotinidase deficiency	Enzyme assays
Ceruloplasmin (113)	Diagnosis of Wilson's disease	LC-MS/MS
Free-β human chorionic gonadotrophin and pappalysin-1 (114)	Assessing fetal aneuploidy risk	DELFIA
Hemoglobin A_2 (115)	Diagnosis of thalassemia	LC-MS/MS
Hypoxanthine-guanine phosphoribosyltransferase, adenine phosphoribosyltransferase, adenosine deaminase (116)	Diagnosis of purine metabolism disorders	Non-radiochemical HPLC
Iduronate 2-sulfatase (117)	Diagnosis of Hunter disease	LC-MS/MS
Acid α-glucosidase (118)	Diagnosis of glycogen storage disease II	Enzyme assays
8 lysosomal enzymes (119)	Clinical differentiation between mucopolysaccharidosis, oligosaccharidosis, and mucolipidosis II and III	Enzyme assays
α-iduronidase activity (120)	Diagnosis of α-L-iduronidase deficiency	Enzyme assays
Phytanic acid and pristanic acid (121)	Diagnosis of peroxisomal disorders	Biochemistry
β-Lipoprotein (122)	Diagnosis of familial type II and combined hyperlipidemia	Electro-immunodiffusion
Fumarylacetoacetase (123)	Diagnosis of hereditary tyrosinemia type I	ELISA
Lysosomal b-d-galactosidase (124)	Diagnosis of mucopolisaccharidosis type I	Enzyme assays
Immunoreactive trypsinogen (125)	Fetal screening for cystic fibrosis	Immunoassay
Galactose-1-phosphate uridyltransferase (126)	Diagnosis of galactosemia	Fluorescent
Phenylalanine (127)	Neonatal screening for phenylketonuria	Densitometry
Homocysteine (128)	Assessment of homocysteinuria	Fluorimetric HPLC method
17-hydroxyprogesterone, androstenedione (129)	Diagnosis of congenital adrenal hyperplasia	LC-MS/MS
Free carnitine (130)	Assessment of inborn errors of metabolism	LC-MS/MS
Guanidinoacetate and creatine (131)	Assessment of primary creatine disorders	FIA-ESI-MS/MS
Mutations of factor V G1691A, prothrombin G20210A, 5′10′ methylenetetrahydrofolate reductase C677T, and methionine synthase A2756G (132)	Assessment of susceptibility to venous thromboembolism	PCR
Mutation c.-32T>G (IVS1-13>G) (133)	Diagnosis of acid maltase deficiency	Real-time PCR
Mutation (IVS4+919G->A) (134)	Diagnosis of Fabry disease	DNA-based assay
Substitution (c.840C>T) (135)	Assessment of spinal muscular dystrophy	DHPLC
Mutation of cystic fibrosis transmembrane conductance regulator (136)	Assessment of cystic fibrosis	PCR
Survival motor neuron (SMN) 1 exon 7 deletions, copy number variations of SMN1 and SMN2 (137)	Assessment of spinal muscular atrophy	PCR
Fragile X mental retardation (FMR) 1 gene methylation (138)	Assessment of fragile X syndrome	PCR

Other

Measure	**Use**	**Method**
Hemoglobin (139)	Variety of clinical uses	Spectrophotometry
Transferrin receptor (140)	Assessment of iron deficiency	ELISA
Retinol (141, 142)	Assessment of vitamin A deficiency	HPLC
Prolactin (143)	Diagnosis of epilepsy	ELISA

Various inflammatory markers (e.g., tumor growth factor-β1 and C-reactive protein) (144)	Assessment of inflammatory status	Luminex
Immunoglobulin E (145)	Assessment of allergic disease and repeated macro-parasitic infections	Enzyme immunoassay
Amino, organic, and fatty acid (146)	Assessment of metabolic disorders	LC-MS/MS
Dichlorodiphenyldichloroethylene (147)	Assessing the level of environmental pollutants in newborns	Capillary gas chromatography