Chapter 23

Public and Population Health Genomics

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Chapter Outline

INTRODUCTION

Population sciences such as epidemiology focus on studying whole populations rather than individuals. Through studying environmental, genomic, and social factors that affect human health, population level interventions can be identified. The social sciences focus on studying society and human behavior through fields such as anthropology, economics, law, psychology, and sociology. The study of the ethical, legal, and social implications (ELSI) of genomics plays an important role in applying genomics to population health.

Although the fields of population genomics and genomic medicine look to prevent or treat disease through different perspectives, they can act complementarily to enhance overall health outcomes for both individuals and populations at large. Population genomics seeks to integrate knowledge from genomic, population, and social sciences to improve population health.

The genomic sciences focus on studying whole genomes, such as the entire DNA sequence making up the human genome. Through studying genomics, genetic variants influencing human health can be identified. Studies of particular genes can then further elucidate the function of genetic variants. The three major disciplines contributing to population genomics (genomics, population science, and social sciences) explore two cross-cutting issues: global health, and population versus individual health. This aspect of the emerging field of population genomics is discussed in this chapter using specific examples from diverse diseases such as breast cancer, colorectal cancer, bronchial asthma, Crohn disease, Alzheimer dementia, and cystic fibrosis.

BREAST CANCER

Around one in nine women worldwide develop breast cancer during their lifetime. A family history of breast cancer along with ovarian cancer may be encountered in approximately 5% of the affected women. A number of disease-causing mutations in the two major genes, *BRCA1* and *BRCA2*, are now recorded worldwide. In addition, several variants may occur in 5–10% of breast cancer cases; these variants are found in less than 1% of the general population [1]. Specific populations, such as those of Ashkenazi Jewish descent, have an increased incidence of *BRCA1* or *BRCA2* variants. Two variants in *BRCA1* and one in *BRCA2* are found at a rate 5 times higher in Ashkenazi Jews than in the general population [2,3].

For these reasons, family members of those with known *BRCA1/2* variants or those with a family history of breast cancer may be offered genetic testing. Men with *BRCA1/2* variants are also at an increased risk of developing breast cancer [4,5]. Thousands of variants have been discovered in *BRCA1* and *BRCA2*, yet only a minority have a known deleterious effect [6]. Genetic testing therefore has the possibility of finding a variant of unknown effect, for which the functional significance is unclear. One recent study found that 10% of women undergoing *BRCA1* and *BRCA2* testing receive an ambiguous test result because of the detection of a variant of unknown significance [7]. Thus although deleterious variants are known to increase the risk of developing breast cancer approximately five-fold, deciding how to react to variants of unknown effect can be challenging for all involved including both clinicians and patients [8].

COLORECTAL CANCER

Genomic information can be used clinically to inform disease risk, diagnosis, drug selection, and drug dosing. Colorectal cancer provides a good example of an area where population level screening along with genomic medicine approaches are coming together to improve overall population health.

Over 1 million individuals are diagnosed with colorectal cancer each year worldwide, accounting for approximately 9–10% of cancer diagnoses in 2008 [9]. It is the third leading cause of cancer-related death in the United States and the fourth worldwide [9,10]. In colorectal cancer, a patient's genomic information can be used to determine risk of inherited colorectal cancer syndromes, whether certain biological agents will work in specific patients, and what starting dose to use on specific chemotherapeutics.

As many as 20–25% of colorectal cancer cases have a family history of colorectal cancer (two or more first-degree relatives with colorectal cancer), yet only 5–6% have an established familial genetic syndrome with a known genetic variant [11,12]. Of those with established familial genetic syndromes, approximately 3% will be diagnosed with Lynch syndrome (including variants in the genes *MLH1, MSH2, MSH6, PMS2*, and *EPCAM*) and 1% with familial adenomatous polyposis (including variants in *APC* and *MUTYH*) [11]. Individuals with a family history of colorectal cancer have a two- to threefold greater risk of developing colorectal cancer than the general population and thus genetic testing for an individual with a known family history has substantial public health benefit [11]. Those with a known family history of colorectal cancer are also recommended for screening at younger ages, typically 10 years younger than the onset of the youngest case in their family.

Genetic testing is also used to determine treatment options in colorectal cancer [11,12] (Table 23.1). For example, genetic variants that make *KRAS* constitutively active have been shown to provide resistance to monoclonal antibodies directed against the upstream epidermal growth factor receptor (EGFR), because both are components of a cellular pathway leading to abnormal cell growth and cancer. Thus cetuximab and panitumumab (anti-EGFR antibodies) are given only to individuals with normally functioning *KRAS*, where blocking EGFR can have an effect [11].

Pharmacogenomics can also be useful in determining drug dosage for colorectal cancer. For example, the FDA recommends testing for *UGT1A1* variants when administering irinotecan, because individuals homozygous or heterozygous for the *UGT1A1*28* allele are at increased risk of developing neutropenia and severe infections [13]. Individuals with inactivating *UGT1A1* variants are therefore recommended to be started at a lower dosage of irinotecan to reduce the risk of neutropenia [13].

In addition to modifying drug dosing, pharmacogenomic information can also be used in drug selection to choose agents more likely to give a beneficial response based on a patient's genetically driven ability to metabolize them. For example, in patients of Asian ancestry given carbamazepine (used to treat epilepsy and bipolar disorder) the *HLA-B*1502* allele has been associated with Stevens-Johnson syndrome/toxic epidermal necrolysis, a life-threatening skin condition. This allele can be found in over 15% of the population in some regions in Asia including Hong Kong, Thailand, Malaysia, and parts of the Philippines, and is very rare in other populations outside Asia [14] (Table 23.2).

Within populations of Asian ancestry, there can also be great variation, such as is seen within China where the *HLA-B*1502* allele prevalence varies from 0 to 36%, depending upon ethnicity. Thus the US Food and Drug

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TABLE 23.1 Pharmacogenomic Variants in Colorectal Cancer [11].

	Function	Consequences
BRAF	Downstream pathways constitutively active	Resistance to anti–epidermal growth factor receptor monoclonal antibodies
ERCC-1	DNA excision repair	Resistance to platinum-based chemotherapy drugs
Interleukin 8	Increased *VEGF* expression	Increased cancer recurrence
KRAS	Downstream pathways constitutively active	Resistance to anti–epidermal growth factor receptor monoclonal antibodies
Microsatellite instability	Reduced DNA repair	Improved prognosis
TSER	Increased or decreased thymidylate synthase, depending on variant	Response to fluorouracil reduced/increased (negative relationship)
UTGA1	Responsible for metabolism of irinotecan	Dosing for irinotecan
VEGF	Increased *VEGF* expression	Increased cancer recurrence

TABLE 23.2 *HLA-B*1502* Allele Prevalence in Worldwide Populations [46].

Population	*HLA-B*1502* Allele Prevalence
China	0–36%
Indonesia	11–17%
Malaysia	21–6%
Vietnam	14%
Thailand	8–9%
India	0–6%
Singapore	6%
Taiwan	4–6%
USA	0–4%
South Korea	0.2–2%
Australia	0–1%
Japan	0.10%
Germany	0%
Brazil	0%
Bulgaria	0%
Burkina Faso	0%
Cuba	0%
Ireland	0%
Italy	0%
Mexico	0%
Morocco	0%
Oman	0%
South Africa	0%

Administration (FDA) recommends genetic testing for the *HLA-B*1502* variant before prescribing carbamazepine for patients of Asian ancestry and for those with one or two copies of the variant only treating with carbamazepine when the benefits outweigh the risks of the drug [14].

Bronchial Asthma

Population variation is an important consideration when studying common complex conditions that are influenced by multiple genetic, environmental, and social risk factors, such as bronchial asthma. Over 300 million individuals of all ages have asthma worldwide [15]. Prevalence estimates can vary greatly by ethnicity; however, from 2% to 33% [16]. In the United States, prevalence ranges from approximately 8% in European Americans to 12% in African

Americans and 7% in Hispanic Americans [17]. Within admixed populations, such as Hispanic Americans, even greater variation can be seen when populations are further substratified, with Mexican American populations around 6%, whereas Puerto Rican populations are closer to 19% [17]. Genetic studies have shown that at least some of this variation is caused by differences in genetic variants, with 35–80% of the variation in asthma heritability explained by genetic factors [18,19]. For example, variants in *ADAM33* have been seen in European, African American, and some Hispanic populations, but not in other European American, Mexican, Puerto Rican, and Korean populations, all of which found different variants in *ADAM33* associated with asthma [20] (Fig. 23.1).

Studying the interplay between environmental, genetic, and social risk factors is also critical to understanding the etiology of this complex disease. For example, the effect of air pollution on asthma case reports is modified by genetic factors as well, showing potential gene–environment interactions. A key measure of air pollution is PM10, the concentration in parts per million of particulate matter 10 μm in diameter or less, which can penetrate and irritate small airways. PM10 has been shown in multiple epidemiological studies to be an independent risk factor for increased respiratory symptoms including asthma [21–25]. Similarly variants in over 100 genes have been associated with asthma in genome-wide association studies (GWASs) [20,26,27]. Looking at the two risk factors together, however, reveals a potential gene–environment interaction where variants in *GSTP1*, *SOD2*, and *NFE2L2*, all related to oxidative stress pathways, were also associated with increased hospital admissions for asthma-related symptoms during days with high PM10 levels [21].

CROHN DISEASE

Genomics can also be used to help identify and better define environmental risk factors in population studies. For example, genomic data profiling the bacteria inhabiting the human gut, or gut microbiome, has revealed differences in the bacterial populations present in individuals with Crohn disease (a form of inflammatory bowel disease) [28]. The genomic signatures of the gut microbiome in patients with Crohn disease shows some bacterial populations to be decreased, whereas others are more abundant [28–31].

ALZHEIMER DEMENTIA

Many genetic loci have also been associated with multiple phenotypes, as evidenced in the National Human Genome Research Institute Catalog of Published GWASs [27,32]. (Fig. 23.2). Such pleiotropic genes (genes associated with multiple phenotypes) can present additional challenges when considering the ELSI of returning genetic testing
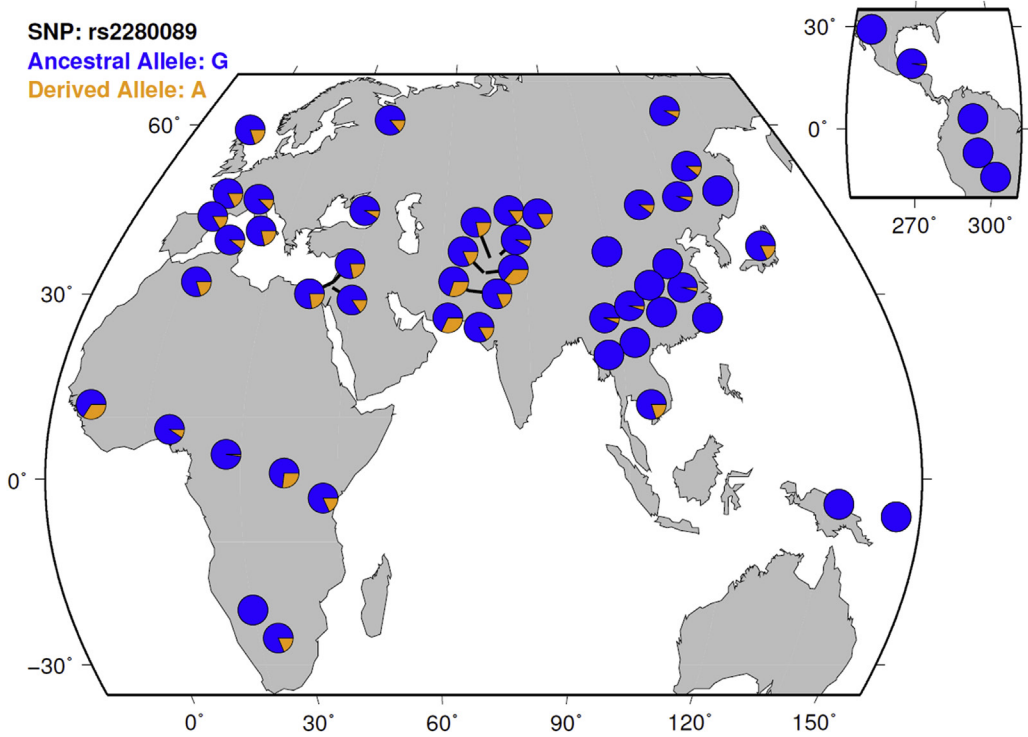
FIGURE 23.1 Example of the variation in allele incidence by population for rs2280089 in *ADAM33*. The *A* allele has been previously associated with predisposition to asthma and bronchial hyperresponsiveness in populations from the United States, United Kingdom, and China [48–51].
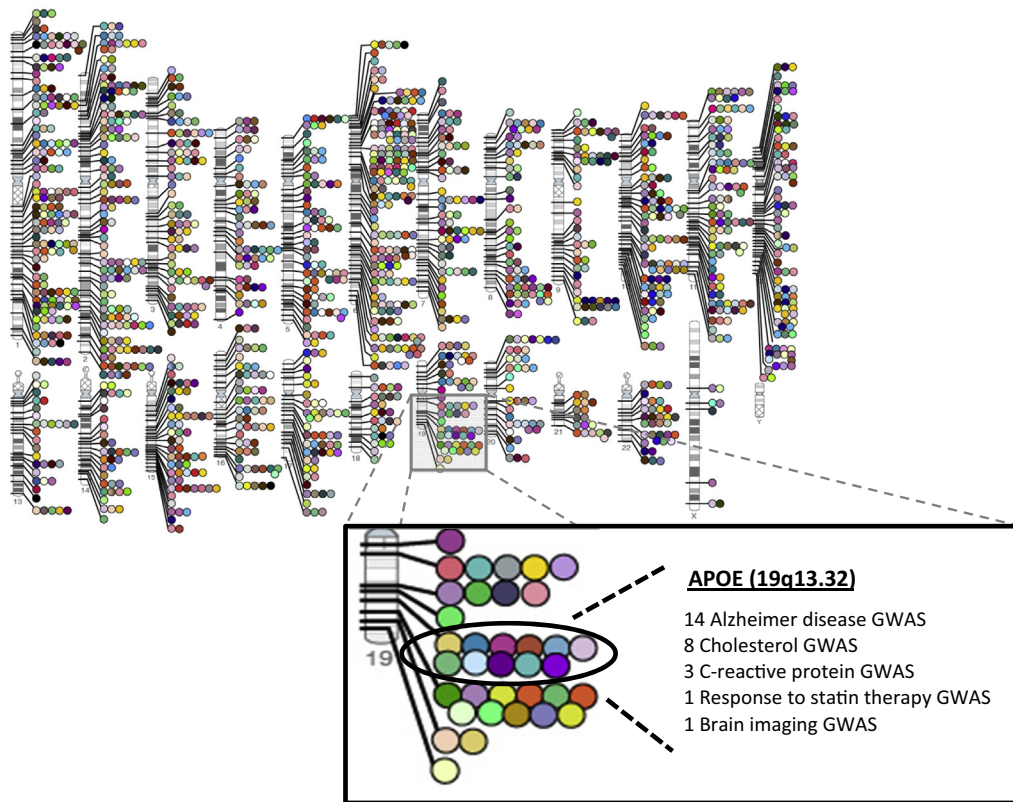

FIGURE 23.2 The National Human Genome Research Institute genome-wide association study *(GWAS)* catalog showing that many genetic loci are associated with multiple phenotypes. *APOE* on 19q13.32 is highlighted along with examples of the disease phenotypes associated with the gene [27].

results. For example, variants in *APOE* are associated with multiple phenotypes, including Alzheimer dementia, cholesterol level, coronary disease, C-reactive protein, hyperlipoproteinemia type III, low-density lipoprotein level, macular degeneration, and response to statin therapy [33]. The *APOE*e4* variant in particular has been associated with increased risk for developing both Alzheimer dementia and atherosclerosis along with a protective effect against developing macular degeneration [33].

CYSTIC FIBROSIS

In many ways the family serves as an intermediary between individual- and population-level views of health. It is an important viewpoint that should be considered in population genomics, because genomic information is inherently relevant not only to the individual tested, but also to their family members with whom they share a large proportion of their genetic variants. How and with whom such family-related health information can or should be shared is an important consideration for advancing both individual and family health.

The availability of genomic information is also blurring the line between population and individual level views of health. For example, genetic testing for cystic fibrosis spans population screening–based carrier, prenatal, and newborn tests to individualized genomic medicine–based diagnostic and pharmacogenomic testing for treatment selection. From the population screening perspective, genetic testing is offered to prospective parents of European decent and others who may be at increased risk of having a child affected by cystic fibrosis, because the prevalence of cystic fibrosis is highest in Northern Europe [34].

Over 1500 variants have been found in the *CFTR* gene, but the functional significance of many is unknown, with the most common variant associated with cystic fibrosis being ΔF508 [34]. In 2012, the FDA approved ivacaftor, the first drug to treat a specific cystic fibrosis variant, G551D in *CFTR* [35,36] (Table 23.3). The G551D variant impairs the ability of the *CFTR* channel to open [34,35,37]. Ivacaftor functions by increasing the likelihood of the *CFTR* channel being open, improving chloride transport and restoring the function of the *CFTR* gene [35–37]. As the cost of genomic

TABLE 23.3 National Heart, Lung, and Blood Institute Exome Sequencing Project Results for African-American and European-American Participants for the G551D Variant (rs75527207) Associated with Cystic Fibrosis [47].

	Allele Count A	Allele Count G
African-American	0	4406
European-American	18	8582

sequencing continues to drop and electronic health records improve, the cost of collecting and interpreting genomic data may fall below the cost of conducting individual genetic tests, further blurring the line between clinical and public health data.

CROSS-CUTTING ISSUES OF POPULATION GENOMICS

Although all three of the population sciences contributing to population genomics work together, there are also some issues that more broadly span the field of population genomics and its relationship to medicine and public health. Touched upon in many of the examples discussed, it is important to consider the broader implications of population genomics to global health and how population and individual level views of health can work together to improve health worldwide.

Cardiovascular disease is a leading cause of death worldwide, with over 13.5 million deaths from ischemic heart disease, stroke, or another form of cerebrovascular disease in 2008, and is highly amenable to study using population genomics techniques [38]. For example, adding rs10757274 genotyping to the Framingham risk score improved its ability to determine individuals who would suffer later cardiovascular events independent of family history [39]. Such models can be used to screen populations to determine individuals at increased risk of disease and recommend further testing and individualized genomic medicine.

Whereas chronic conditions such as cardiovascular disease make up the majority of deaths in the developed world, infections are still a major health concern within developing countries and are equally amenable to study using population genomics. Genomics has made possible the rapid identification of the organisms causing recent pandemic outbreaks including H1N1 and severe acute respiratory syndrome, as well as identifying the source of foodborne illness. The availability of genomic sequence information on malaria parasites, mosquito vectors, and their human hosts are all being leveraged to produce more rapid diagnosis and better drugs, vaccines, and intervention strategies to fight malaria [40,41].

To maximize the benefit of population genomics advances to global health, it is also important to include multiple populations of diverse age, ethnicity, and gender in disease research. As evidenced by the example of asthma genomics, the prevalence of disease can be highly variable across ancestral groups and genetic variants often vary in incidence as well. Thus although a single pathway may be implicated in disease across many populations, the most common variant in each population may lie in different genes or gene regions.

Local environmental and social factors that impact disease and population health should also be incorporated into
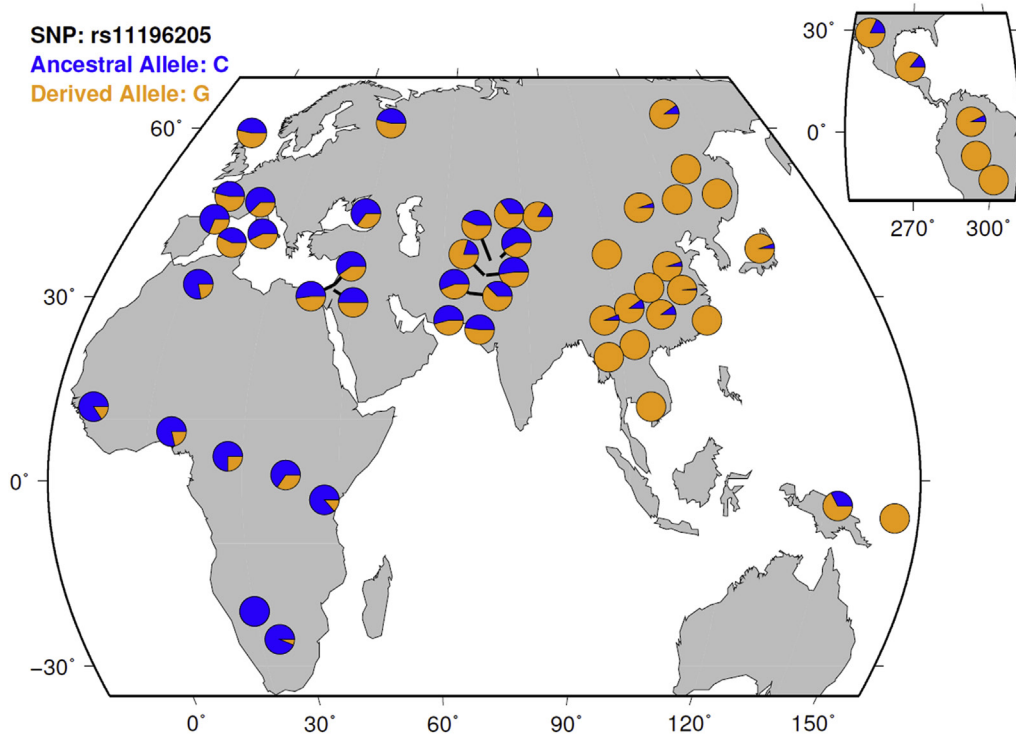
FIGURE 23.3 Example of the variation in allele frequency by population for rs11196205 in *TCF7L2*, a single nucleotide polymorphism previously associated with type 2 diabetes mellitus risk [44,48].

studies of population genomics to produce the most complete picture of disease etiology. For example, the prevalence of type 2 diabetes mellitus is increasing globally and has been associated with multiple genetic (more than 60 genes to date), epigenetic (such as methylation or histone modification), environmental (such as diet), and social factors (such as exercise), all of which contribute to this complex disease [42]. The prevalence of type 2 diabetes mellitus varies by country from approximately 5–29%, with risk alleles such as the C allele in rs11196205 decreasing in incidence from sub-Saharan Africa to Asia (Fig. 23.3) [43,44]. Effects of other risk factors also vary across different populations, with the relative risk of type 2 diabetes mellitus for each $5 \, \text{kg/m}^2$ increase in body mass index; for example, being 2.4 in Asian Americans, 2.2 in Hispanic Americans, 2.0 in European Americans, and 1.6 in African Americans [45].

SUMMARY

In this chapter we have explored how the integration of genomic, population, and social sciences in population genomics can improve health through examples in pharmacogenomics, population variation, and genetic pleiotropy. We have also investigated cross cutting issues in global health and population versus individual health where population genomics can play a crucial role in the translation of genomic health discoveries worldwide and population

screening can work together with genomic medicine to provide the greatest health benefit to both individuals and populations at large. Thus, multidisciplinary research in population genomics, can improve clinical care through understanding of the genetic variation in populations that contributes to complex disease.

REFERENCES

[1] Schwartz GF, Hughes KS, Lynch HT, et al. Proceedings of the International Consensus Conference on Breast Cancer Risk, Genetics, & Risk Management, April, 2007. Cancer November 15, 2008;113(10):2627–37.

[2] Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N Engl J Med May 15, 1997;336(20):1401–8.

[3] Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of *BRCA1* and *BRCA2* gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst July 21, 1999;91(14):1241–7.

[4] Thompson D, Easton DF. Cancer incidence in *BRCA1* mutation carriers. J Natl Cancer Inst September 18, 2002;94(18):1358–65.

[5] Cancer risks in *BRCA2* mutation carriers: the Breast Cancer Linkage Consortium. J Natl Cancer Inst August 4, 1999;91(15):1310–6.

[6] An open access on-line breast cancer mutation data base. http://research.nhgri.nih.gov/bic/?CFID=313172&CFTOKEN=38988484.

[7] Peshkin BN, DeMarco TA, Brogan BM, Lerman C, Isaacs C. *BRCA1/2* testing: complex themes in result interpretation. J Clin Oncol May 1, 2001;19(9):2555–65.

[8] Howlader N, Noone A, Krapcho M, et al, editors. Seer cancer statistics review, 1975–2009 (Vintage 2009 populations). Bethesda, MD: National Cancer Institute; 2012. http://seer.cancer.gov/csr/1975_2009_pops09/. [accessed 27.06.12].

[9] Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer March 1, 2013;132(5):1133–45. http://dx.doi.org/10.1002/ijc.27711. Epub 2012 Jul 26.

[10] Society AC. Cancer facts & figures 2012. 2012. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. [accessed 27.06.12].

[11] Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. Lancet March 20,2010;375(9719):1030–47.

[12] Gala M, Chung DC. Hereditary colon cancer syndromes. Semin Oncol August 2011;38(4):490–9.

[13] Administration UFaD. Dugs@FDA: irinotecan label and approval history. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory - labelinfo.

[14] Administration UFaD. Drugs@FDA: carbamazepine label and approval history. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

[15] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy May 2004;59(5):469–78.

[16] Sembajwe G, Cifuentes M, Tak SW, Kriebel D, Gore R, Punnett L. National income, self-reported wheezing and asthma diagnosis from the world health survey. Eur Respir J February 2010;35(2):279–86.

[17] Current asthma prevalence percents by age. United States: National Health Interview Survey (NHIS) Data; 2010. http://www.cdc.gov/asthma/nhis/2010/table4-1.htm.

[18] Nieminen MM, Kaprio J, Koskenvuo M. A population-based study of bronchial asthma in adult twin pairs. Chest July 1991;100(1):70–5.

[19] Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. Am Rev Respir Dis December 1990;142(6 Pt 1):1351–8.

[20] Drake KA, Galanter JM, Burchard EG. Race, ethnicity and social class and the complex etiologies of asthma. Pharmacogenomics April 2008;9(4):453–62.

[21] Canova C, Dunster C, Kelly FJ, et al. PM10-induced hospital admissions for asthma and chronic obstructive pulmonary disease: the modifying effect of individual characteristics. Epidemiology July 2012;23(4):607–15.

[22] Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO_2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. Environ Health Perspect April 2010;118(4):449–57.

[23] Preutthipan A, Udomsubpayakul U, Chaisupamongkollarp T, Pentamwa P. Effect of PM10 pollution in Bangkok on children with and without asthma. Pediatr Pulmonol March 2004;37(3):187–92.

[24] Gordian ME, Choudhury AH. PM10 and asthma medication in school children. Arch Environ Health January 2003;58(1):42–7.

[25] Donaldson K, Gilmour MI, MacNee W. Asthma and PM10. Respir Res 2000;1(1):12–5.

[26] Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun March 2006;7(2):95–100.

[27] Hindorff LA, Sethupathy P, Junkins HA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci USA June 9, 2009;106(23):9362–7.

[28] Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis May 2012;18(5):968–84.

[29] Frank DN, Robertson CE, Hamm CM, et al. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. Inflamm Bowel Dis January 2011;17(1):179–84.

[30] Walker AW, Sanderson JD, Churcher C, et al. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. BMC Microbiol 2011;11:7.

[31] Gophna U, Sommerfeld K, Gophna S, Doolittle WF, Veldhuyzen van Zanten SJ. Differences between tissue-associated intestinal microfloras of patients with Crohn's disease and ulcerative colitis. J Clin Microbiol November 2006;44(11):4136–41.

[32] Sivakumaran S, Agakov F, Theodoratou E, et al. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet November 11, 2011;89(5):607–18.

[33] Apolipoprotein E. Online Mendelian Inheritance in Man. OMIM; 2012. http://omim.org/entry/107741?search=APOE&highlight=apoe - contributors-shutter. [accessed 24.06.12].

[34] O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet May 30, 2009;373(9678):1891–904.

[35] Davis PB, Yasothan U, Kirkpatrick P. Ivacaftor. Nat Rev Drug Discov May 2012;11(5):349–50.

[36] Administration UFaD. Drugs@FDA: ivacaftor label and approval history. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory - labelinfo.

[37] Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell function in vitro by a *CFTR* potentiator, VX-770. Proc Natl Acad Sci U. S. A November 3, 2009;106(44):18825–30.

[38] Death: Top 10 Causes. WHO Factsheet. http://www.who.int/mediacentre/factsheets/fs310/en/index.html.

[39] Talmud PJ, Cooper JA, Palmen J, et al. Chromosome 9p21.3 coronary heart disease locus genotype and prospective risk of CHD in healthy middle-aged men. Clin Chem March 2008;54(3):467–74.

[40] Volkman SK, Neafsey DE, Schaffner SF, Park DJ, Wirth DF. Harnessing genomics and genome biology to understand malaria biology. Nat Rev Genet May 2012;13(5):315–28.

[41] Agnandji ST, Lell B, Soulanoudjingar SS, et al. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med November 17, 2011;365(20):1863–75.

[42] McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med December 9, 2010;363(24):2339–50.

[43] Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet July 2, 2011;378(9785):31–40.

[44] Chen R, Corona E, Sikora M, et al. Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases. PLoS Genet April 2012;8(4):e1002621.

[45] Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care July 2006;29(7):1585–90.

[46] Gonzalez-Galarza FF, Christmas S, Middleton D, Jones AR. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. Nucleic Acids Res January 2011;39(Database issue):D913–9.

[47] Exome Variant Server. http://evs.gs.washington.edu/EVS/.

[48] Li JZ, Absher DM, Tang H, et al. Worldwide human relationships inferred from genome-wide patterns of variation. Science February 22, 2008;319(5866):1100–4.

[49] Raby BA, Silverman EK, Kwiatkowski DJ, Lange C, Lazarus R, Weiss ST. *ADAM33* polymorphisms and phenotype associations in childhood asthma. J Allergy Clin Immunol June 2004;113(6):1071–8.

[50] Qu S, Sun D, Wang Y, Zhang C, Lv Y, Yao L. Association of *ADAM33* polymorphisms with childhood asthma in a northern Chinese population. Exp Mol Pathol December 2011;91(3):775–9.

[51] Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the *ADAM33* gene with asthma and bronchial hyperresponsiveness. Nature July 25, 2002;418(6896):426–30.