

## Review Article

DOI: 10.22114/ajem.v0i0.216

# The Current Status of Genes and Genetic Testing in Emergency Medicine: A Narrative Review

Seyed Mohammad Kazem Aghamir<sup>1</sup>, Mehdi Ebrahimi<sup>2</sup>, Fatemeh Khatami<sup>1\*</sup>

1. Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran.

2. Department of Internal Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.

\*Corresponding author: Fatemeh Khatami; Email: f-khatami@alumnus.tums.ac.ir

Published online: 2019-08-25

## Abstract

**Context:** An emergency is any medical problem that could cause death or permanent injury if not treated quickly. In some occasions, the kind of urgent intervention depends on patient's exact genetic background. Unfortunately, the importance of genes in medical emergencies has been forgotten in recent decades.

**Evidence acquisition:** In order to find relevant articles, we searched two databases of Pubmed and Embase. The exact words of "genes", "genetics", "epigenetics", "DNA", and "emergency" were used alone and in combination. All studies like randomized clinical trials (RCT), case/controls, case series, case reports, and review articles were studied to find the related data. No time limitation was considered for the studies.

**Results:** Several aspects of genetic testing are newly considered in emergency departments including cell-free DNA (cfDNA) for disease diagnosis, pharmacogenetics for decreasing the adverse drug effects, and personalized medicine for exact emergency interventions in diseases like Vascular Ehlers-Danlos syndrome (vEDS). Data from genetic testing and genome wide association studies have yielded promising results to make medical emergency interventions more beneficial in the near future.

**Conclusion:** Taking everything into consideration, several advanced genetic and epigenetic alteration technologies can change emergency medicine for the better. Personalized genetic data of patients can turn emergency medicine to personalized medicine.

**Key words:** Emergency Medicine; Pharmacogenetics; Precision Medicine

**Cite this article as:** Aghamir SMK, Ebrahimi M, Khatami F. The Current Status of Genes and Genetic Testing in Emergency Medicine: A Narrative Review. *Adv J Emerg Med.* 2020;4(1):e10.

## CONTEXT

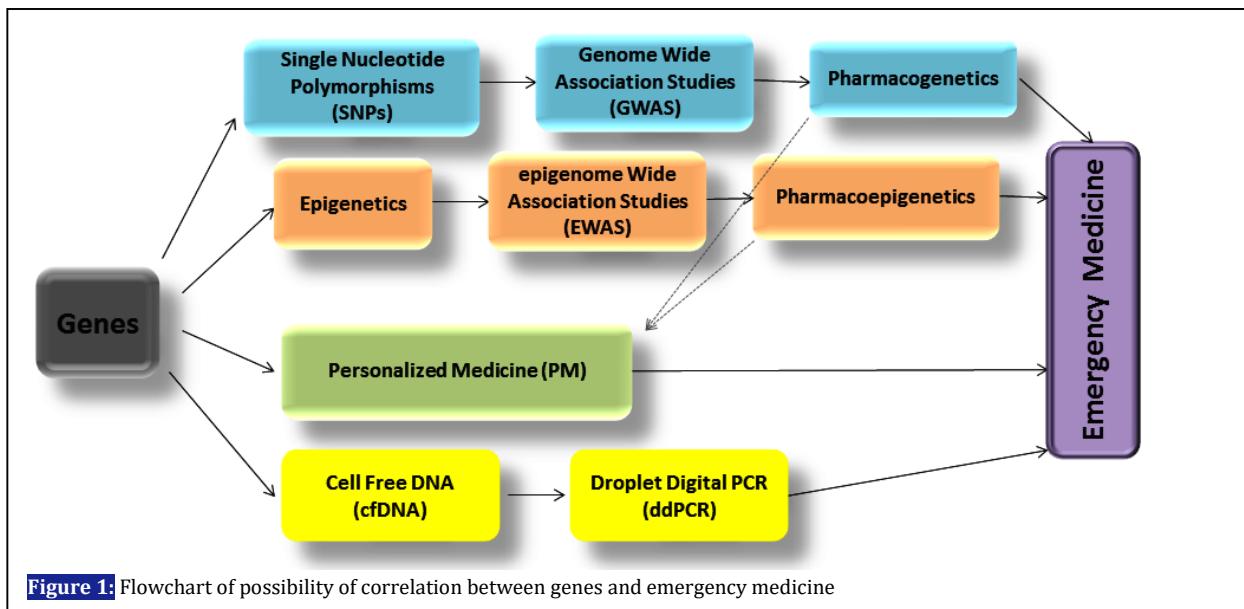
An emergency is a medical problem that is lethal, life-threatening or limb-threatening if not treated quickly. Emergency management usually depends on known procedures based on most frequent cases and common treatment strategies, but it is shifting toward personalized medicine (1, 2). An emergency needs critical interventions to save patients' life, so it is thought that genetic tests are not important in such situations. However, patient's genetic information has just become considerably important even in medical emergencies. Through illustration, genetic information of newborn babies can improve prediction of drug-related complications as essentials of medical emergencies. Novel aspects of pharmacogenomics and genetic testing can cease the adverse drug reactions and subsequently decrease referrals to the emergency room (3). Genetic testing is currently used in emergency room for disease diagnosis through cell-free DNA (cfDNA), for decreasing the adverse drug effects through pharmacogenetics, and for exact

emergency interventions through personalized medicine (4).

Several studies have focused on the fact that personalized clinical protocols can increase the decision making quality about the individual risk stratification and treatment of candidates for renal transplant, patients with drug-related complications, and even newborn urgent interventions (Figure 1) (5). In this review, we present an overview of genetic modifications and the importance of genetic testing in medical emergencies.

## EVIDENCE ACQUISITION

In order to find relevant articles, we searched two databases of Pubmed and Embase. The exact words of "genes", "genetics", "epigenetics", "DNA", and "emergency" were used alone and in combination with each other. All studies like randomized clinical trials (RCT), case/controls, case series, case reports, and review articles were studied to find the related data. No time limitation was considered for the studies.



**Figure 1:** Flowchart of possibility of correlation between genes and emergency medicine

## RESULTS

### *Understanding genomics, pharmacogenomics and personalized medicine*

Deoxyribonucleic acid (DNA) is a molecule made of two chains that coil around each other to form a double helix from the extensive sequence of triplets of different arrangements of four nucleotides (A; adenine, T; thymine, C; cytosine, and G; guanine). Every three nucleotides is called a codon, which is transcribed into RNA during the gene expression process (first hnRNA including introns and exons and then mRNA), and then mRNA is translated into amino acids which finally form functional proteins (6). Any changes in the normal sequence of DNA (mutation) or epigenetic changes influencing gene expression with no changes in the DNA sequence can lead to diseases (7). Genetic changes can happen as the single nucleotide polymorphisms (SNPs), which means common mutations in more than 1% of the population. SNPs are present all over the human genome, both in coding (exons) and noncoding (introns) regions of DNA (8). The Human Genome Project which aimed to sequence the entire human genome was completed in 2003. This project required 13 years, multiple research institutions processing samples, and \$2.7 billion (9). So far, about three million recorded SNPs have been recognized or proposed as responsible for different diseases. A genome-wide association study (GWA study, or GWAS), also known as whole genome association study (WGA study, or WGAS), was developed as an observational study of a genome-wide set of genetic variants in dissimilar persons to observe if any variant is connected with a trait. GWASs typically focus on associations

between single-nucleotide polymorphisms (SNPs) and traits like major human diseases, but can equally be applied to any other genetic variants and any other organisms (10). The set of web-based SNP selection tools (freely available at <http://www.niehs.nih.gov/snpinfo>) is valid to analyze the linkage regions and select SNPs based on GWAS results, linkage disequilibrium (LD), and predicted functional characteristics of both coding and non-coding SNPs (11). Different responses of several patients with the same disorders to the same medication is under their genetic information like SNPs. The new concept of personalized medicine or precision medicine (PM) has been developed over the last decade so that optimal therapies can be chosen based on the setting of a patient's genetic content or other molecular or cellular analyses (12, 13). Genetic information is main aspect of personalized medicine, that is, pharmacogenomics, which includes all sorts of personalization measures. The Pharmacogenomics Knowledgebase (PharmGKB) is a source of accurate information, and distributes information about the impression of human genetic variations (SNPs) on drug responses (14).

### *Different types of genetic testing*

Genetic tests look at person's gene alterations at DNA sequence level as a genetic modification, at mRNA level (gene expression), microRNA expression, or variations in the quantity, role, or structure of key proteins coded by specific genes (15). Testing the DNA can be at chromosomal level, for DNA studies, or biochemical genetic studies. At chromosomal level, cytogenetics is described as the reading of chromosomes under the microscope.

Stained chromosomes look like the ropes with alternative light and dark bands. An image (an actual photograph from one cell) of all 46 chromosomes in their pairs is called a karyotype. The number and structure of the chromosomes can be checked and additional abnormal chromosomes or deletions can be detected. Cytogenetic studies are possible over the blood sample, prenatal sample, and tissue biopsies (16, 17). Genes can be genetically and epigenetically studied through DNA analysis to examine if the DNA consensus sequences are correct with no changes in gene expression or in the alphabet of DNA. DNA modifications can be DNA duplications, DNA deletions, point mutations as nucleotides change or DNA repeats. Throughput techniques of DNA sequencing like next-generation sequencing (NGS) technologies and exome sequencing have recently made it possible to examine the whole genome and all exons as fast as possible (18-20). More than checking the DNA sequence, it is possible to perform protein truncation studies (considering protein shorter than normal size as the result of converting a coding trinucleotide to stop codon). Sometimes, a mutation in a gene yields a protein that is truncated and nonfunctional with abnormal folding and wrong 3D structure (21-23).

#### ***Emergency tests based on DNA***

Although molecular tests do not find their exact position at medical emergency, there are some reports. For examples, biomarkers and genetic data in the field of infection diagnostic tests in an emergency medicine (24). In patients with  $\geq 2$  Systemic Inflammatory Response Syndrome (SIRS) principles and medical symptoms of infection at the emergency department of Jeroen Bosch Hospital, Netherlands, the amount of C-reactive protein (CRP), neutrophil-lymphocyte count ratio (NLCR), procalcitonin (PCT) and soluble urokinase plasminogen activator receptor (suPAR) were evaluated. For this purpose, 1 ml EDTA blood was collected and selective pathogen DNA isolation was performed with MolYsis (Molzym). In fact, Van den Brule and his colleagues suggested that molecular assays NLCR is a cheap, fast, easy to define biomarker for pathogen identification using molecular diagnostics (24). There is another report on the plasma nuclear and mitochondrial DNA (mtDNA) quantity as the forecasters of outcome in patients with severe sepsis in the emergency room in Taiwan (25). Sepsis is the presence of dangerous microorganisms in patients' blood or other tissues and the body's response to their presence, potentially leading to the malfunctioning of various organs, shock, and death (26). Despite the

development of clinical practice guidelines in a several areas related to infections and sepsis, the rate of death from sepsis is still high (27, 28). Kung and colleagues designed the prognostic importance of circulating plasma DNA levels in patients with severe sepsis. They studied over 67 patients to determine their plasma DNA levels by real-time quantitative polymerase chain reaction assay (RT-PCR). They suggested the level of plasma mitochondrial DNA as a more potent predictor than lactate concentration or sequential organ failure assessment (SOFA) score on admission. Vascular Ehlers-Danlos syndrome (vEDS) is a disease with arterial, intestinal, and/or uterine fragility, thin and translucent skin, and easy bruising (29). More often than not, vEDS patients are trained to apply urgent medical attention for sudden, unexplained pain. They can be under medical or surgical management for arterial complications, bowel rupture, or uterine rupture during pregnancy. It is diagnosed in relatives by documentation of a heterozygous pathogenic variant in COL3A1 gene (Collagen Type III Alpha 1 Chain) (30, 31). Depending on the disease, taking the right kind of emergency measure may result in life or death. For vEDS, due to the complicated disease signs, emergency interventions can simply move in the wrong way. So it is suggested that patients provide related genetic testing information to the emergency physician.

#### ***Cell-free plasma DNA in medical emergency***

Cell-free DNA (cfDNA) is a short fragment of DNA (about 200 nucleotides) released from dead cells following necrosis or apoptosis. Actually, cfDNA are representative of genetic and epigenetic nature of cells and a perfect non-invasive tool for real-time analysis of the body especially in malignancies (32-34). Both quantitative and mutation cfDNA can provide essential information about diseases and require digital droplet PCR (ddPCR) and ultra-deep sequencing technology (35, 36). This new technique is usually applied for cfDNA characterizations with outstanding sensitivity and specificity. Contrary to NGS that is linked to high error rates in cfDNA (error rates range roughly from 0.1% to 1%) (37, 38). For cfDNA analysis, the incorporation of unique identifiers (UIDs) during library preparation is recommended (39, 40). Recently, some benefits of cfDNA have been suggested for medical emergency. Fever (pyrexia) up to 103 °F (39.4 °C) is not an emergency in adults, but is a sign of infection in infants, and on occasions, it can be an indicator of other underlying diseases like immune-mediated and neoplastic conditions in adult, as well. Srugo et al. issued the

novel tool for discrimination of bacterial and viral infections in children at five pediatric emergency departments (41). They suggested that this novel assay was considerably more precise than CRP, procalcitonin, and routine laboratory parameters. Additionally, a systematic review and meta-analysis by Hoeboer et. al. investigated the diagnostic accuracy of PCT for bacteremia (42). In emergency cases, the normal concentrations of cfDNA can eliminate the presence of an infection in febrile patients while high concentrations of cfDNA and its increase to ten times indicate severity of infections (43). Both quick Sequential Organ Failure Assessment (qSOFA) score and cfDNA are prognostic markers in patients with infection (44). Jackson Chornenki and his colleagues showed that the origin and mechanism of release of cfDNA change in patients with trauma and sepsis (45). In sepsis, cfDNA is possibly released by activated neutrophils through the process of NETosis, while cfDNA is released from injured or necrotic cells and does not seem to have prognostic value in trauma patients.

#### ***Personalized medicine and pharmacogenomics in medical emergency***

Adverse drug events happened in 13.5 million outpatient and emergency department visits over a recent 3-year period, with older adults as mainly vulnerable (46). The new knowledge of pharmacogenetics has considerably impacted the progress in identifying genetic risk factors for idiosyncratic adverse drug reactions over the last three decades (47). Pharmacogenetics and pharmacogenomics have been extensively known as central steps of personalized medicine because they consider the genetic information to aim at the best treatment strategy for each patient. Personalized medicine is a medical model that divides people into different subgroups regarding their genetic map for medical interventions. However, not many written documents exist regarding how personalized medicine can change emergency care. It can be expected that recent breakthrough in genetic testing techniques can lead to characterizing patients in completely individualized diagnosis and treatment (48). The rational and careful use of pharmacogenetics can improve drug choice by increasing the effectiveness and lessen harmful side effects. A report by Elliott in polypharmacy patients under home health management indicated that pharmacogenetic testing joined guidance to form a clinical decision support tool (CDST) on reducing drug, gene, and cumulative interaction risk, and it can offer noteworthy insights in prescription drug

treatment and decreasing re-hospitalization and emergency department visits (49).

#### **DISCUSSION**

The new advanced techniques in genetic variations and polymorphism studies together with epigenetic studies have resulted in WGAS and EWAS. They improve the knowledge of disease precision medicine and prediction of medication efficacy in different patients. Pharmacogenetics is the exact knowledge of making a bridge between genetic and drug efficacy, side effects, and complications regarding each person's genetic information and is recently considered in emergency medicals. The new techniques of sequencing like NGS, exome sequencing, methylation specific sequencing, and ddPCR make it possible to have huge genetic and epigenetic information that can be used in emergency room. Recent discovery of cfDNA can help clinicians to make more accurate decision for inflammatory diseases, stroke, and cancers. However, optimization of emergency medicine based on patient's genetic and epigenetic details need time. Recent advances in molecular biology will soon bring the personalized emergency medicine into the practice. In Systemic Inflammatory Response Syndrome (SIRS), mitochondrial DNA in sepsis, Vascular Ehlers-Danlos syndrome (vEDS) based on variant in COL3A1 gene are pacemaker in this way.

#### **CONCLUSIONS**

Taking everything into consideration, several advanced genetic and epigenetic alteration technologies can change emergency medicine for the better. Personalized genetic data of patients can turn emergency medicine to personalized medicine.

#### **ACKNOWLEDGEMENTS**

Special thanks to the Urology Research Center (URC), Sina Hospital.

#### **AUTHORS' CONTRIBUTION**

SMK-A was the principle investigator who conceived and designed the study; M-E developed the study and performed search; and F-K wrote the manuscript.

#### **Conflict OF INTEREST**

All authors declare no conflict of interest for this study.

#### **FUNDING**

None declared.

**REFERENCE**

1. Chittaro L, Carchietti E, De Marco L, Zampa A. Personalized emergency medical assistance for disabled people. *User Model User-Adap Inter.* 2011;21(4-5):407-40.
2. Desierto DA. Necessity and national emergency clauses: sovereignty in modern treaty interpretation. Brill Nijhoff; 2012.
3. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA.* 2001;286(18):2270-9.
4. Callegari C, Isella C, Caselli I, Poloni N, Ielmini M. Pharmacogenetic Tests in Reducing Accesses to Emergency Services and Days of Hospitalization in Bipolar Disorder: A 2-Year Mirror Analysis. *J Pers Med.* 2019;9(2):E22.
5. Schuetz P, Haubitz S, Mueller B. Do sepsis biomarkers in the emergency room allow transition from bundled sepsis care to personalized patient care? *Curr Opin Crit Care.* 2012;18(4):341-9.
6. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA.* 2001;285(5):540-4.
7. Rando OJ, Verstrepen KJ. Timescales of genetic and epigenetic inheritance. *Cell.* 2007;128(4):655-68.
8. Christensen K, Murray JC. What genome-wide association studies can do for medicine. *N Engl J Med.* 2007;356(11):1094-7.
9. Hood L, Rowen L. The human genome project: big science transforms biology and medicine. *Genome Med.* 2013;5(9):79.
10. Ikram MK, Xueling S, Jensen RA, Cotch MF, Hewitt AW, Ikram MA, et al. Four novel Loci (19q13, 6q24, 12q24, and 5q14) influence the microcirculation in vivo. *PLoS Genet.* 2010;6(10):e1001184.
11. Xu Z, Taylor JA. SNPInfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. *Nucleic Acids Res.* 2009;37(Web Server issue):W600-5.
12. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med.* 2010;363(4):301-4.
13. Jain K. Personalized medicine. *Curr Opin Mol Ther.* 2002;4(6):548-58.
14. Whirl-Carrillo M, McDonagh EM, Hebert J, Gong L, Sangkuhl K, Thorn C, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012; 92(4): 414-7.
15. Burke W. Genetic testing. *N Engl J Med.* 2002;347(23):1867-75.
16. Wang T-L, Maierhofer C, Speicher MR, Lengauer C, Vogelstein B, Kinzler KW, et al. Digital karyotyping. *Proc Natl Acad Sci U S A.* 2002;99(25):16156-61.
17. Norton ME, Kuller JA, Dugoff L. *Perinatal Genetics:* Elsevier Health Sciences; 2019.
18. Metzker ML. Sequencing technologies—the next generation. *Nat Rev Genet.* 2010;11(1):31-46.
19. Shendure J, Ji H. Next-generation DNA sequencing. *Nat Biotechnol.* 2008;26(10):1135-45.
20. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med.* 2013;369(16):1502-11.
21. Kenneth Jr M, LeGrand SM. The protein folding problem and tertiary structure prediction: Springer Science & Business Media; 2012.
22. Onuchic JN, Wolynes PG. Theory of protein folding. *Curr Opin Struct Biol.* 2004;14(1):70-5.
23. Mallamace F, Corsaro C, Mallamace D, Vasi S, Vasi C, Baglioni P, et al. Energy landscape in protein folding and unfolding. *Proc Natl Acad Sci U S A.* 2016;113(12):3159-63.
24. Loonen AJ, de Jager CP, Tosserams J, Kusters R, Hilbink M, Wever PC, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. *Plos one.* 2014;9(1):e87315.
25. Kung C-T, Hsiao S-Y, Tsai T-C, Su C-M, Chang W-N, Huang C-R, et al. Plasma nuclear and mitochondrial DNA levels as predictors of outcome in severe sepsis patients in the emergency room. *J Transl Med.* 2012;10(1):130.

26. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39(2):165-228.
27. Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JÁ, Gordo F, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. *Crit Care Med.* 2007;35(5):1284-9.
28. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348(2):138-50.
29. Pepin MG, Murray ML, Byers PH. Vascular Ehlers-Danlos syndrome. *GeneReviews®[Internet]*: University of Washington, Seattle; 2015.
30. Watanabe A, Kosho T, Wada T, Sakai N, Fujimoto M, Fukushima Y, et al. Genetic aspects of the vascular type of Ehlers-Danlos syndrome (vEDS, EDSIV) in Japan. *Circ J.* 2007;71(2):261-5.
31. Frank M, Albuisson J, Ranque B, Golmard L, Mazzella J-M, Bal-Theoleyre L, et al. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers–Danlos syndrome. *Eur J Hum Genet.* 2015;23(12):1657-64.
32. Kahlert C. Liquid Biopsy: Is There an Advantage to Analyzing Circulating Exosomal DNA Compared to cfDNA or Are They the Same? *Cancer Res.* 2019;79(10):2462-5.
33. Volik S, Alcaide M, Morin RD, Collins C. Cell-free DNA (cfDNA): clinical significance and utility in cancer shaped by emerging technologies. *Mol Cancer Res.* 2016;14(10):898-908.
34. Diaz IM, Nocon A, Mehnert DH, Fredebohm J, Diehl F, Holtrup F. Performance of Streck cfDNA blood collection tubes for liquid biopsy testing. *PLoS One.* 2016;11(11):e0166354.
35. Hindson BJ, Ness KD, Masquelier DA, Belgrader P, Heredia NJ, Makarewicz AJ, et al. High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem.* 2011;83(22):8604-10.
36. Hayden R, Gu Z, Ingersoll J, Abdul-Ali D, Shi L, Pounds S, et al. Comparison of droplet digital PCR to real-time PCR for quantitative detection of cytomegalovirus. *J Clin Microbiol.* 2013;51(2):540-6.
37. Quail MA, Kozarewa I, Smith F, Scally A, Stephens PJ, Durbin R, et al. A large genome center's improvements to the Illumina sequencing system. *Nat Methods.* 2008;5(12):1005-10.
38. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, et al. Melanomas acquire resistance to B-RAF (V600E) inhibition by RTK or N-RAS upregulation. *Nature.* 2010;468(7326):973-7.
39. Jabara CB, Jones CD, Roach J, Anderson JA, Swanstrom R. Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID. *Proc Natl Acad Sci U S A.* 2011;108(50):20166-71.
40. Kinde I, Wu J, Papadopoulos N, Kinzler KW, Vogelstein B. Detection and quantification of rare mutations with massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2011;108(23):9530-5.
41. Srugo I, Klein A, Stein M, Golan-Shany O, Kerem N, Chistyakov I, et al. Validation of a novel assay to distinguish bacterial and viral infections. *Pediatrics.* 2017;140(4):e20163453.
42. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AJ. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2015;21(5):474-81.
43. Moreira VG, Prieto B, Rodriguez JS, Alvarez FV. Usefulness of cell-free plasma DNA, procalcitonin and C-reactive protein as markers of infection in febrile patients. *Ann Clin Biochem.* 2010;47(Pt 3):253-8.
44. Rannikko J, Seiskari T, Huttunen R, Tarkiainen I, Jylhävä J, Hurme M, et al. Plasma cell-free DNA and qSOFA score predict 7-day mortality in 481 emergency department bacteraemia patients. *J Intern Med.* 2018;284(4):418-26.
45. Chornenki NLJ, Coke R, Kwong AC, Dwivedi DJ, Xu MK, McDonald E, et al. Comparison of the source and prognostic utility of cfDNA in trauma and sepsis. *Intensive Care Med Exp.* 2019;7(1):29.
46. Gabe ME, Davies GA, Murphy F, Davies M, Johnstone L, Jordan S. Adverse drug reactions: treatment burdens and nurse-led medication monitoring. *J Nurs Manag.* 2011;19(3):377-92.
47. Daly AK. Pharmacogenomics of adverse drug reactions. *Genome Med.* 2013;5(1):5.
48. Limkakeng AT, Jr., Monte AA, Kabrhel C, Puskarich M, Heitsch L, Tsalik EL, et al. Systematic Molecular Phenotyping: A Path Toward Precision Emergency Medicine? *Acad Emerg Med.* 2016;23(10):1097-106.

49. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PloS one*. 2017;12(2):e0170905.