

BEYOND TRADITIONAL DENTISTRY: THE RISE OF GENOMIC AND PERSONALIZED ORAL HEALTH

Laurențiu-Camil Bohîlțea^{1,†}, Claudia Florina Bogdan-Andreescu^{2,†}, Cristina-Crenguța Albu³, Alexandru Burcea^{2,*}, Cristian-Viorel Poalelungi^{4,*}, Andreea Mariana Bănățeanu², Tudor Petru Ionescu²

¹“Carol Davila” University of Medicine and Pharmacy Bucharest, Romania, Faculty of Medicine, Department of Medical Genetics

²“Titu Maiorescu” University, Bucharest, Romania, Department of Speciality Disciplines

³“Carol Davila” University of Medicine and Pharmacy Bucharest, Romania, Faculty of Dentistry, Department of Genetics

⁴“Carol Davila” University of Medicine and Pharmacy, Faculty of Medicine, Department 13

Corresponding authors; *e-mail*: alexandru.burcea@prof.utm.ro, cristian.poalelungi@umfcd.ro;

[†] These authors contributed equally to this work.

ABSTRACT

Recent advancements in genetics have significantly reshaped the landscape of dentistry, providing insights that pave the way for precision oral healthcare. This article explores the critical role of genetics in the diagnosis, prevention, and treatment of oral diseases. By integrating genetic markers and next-generation sequencing (NGS) technologies, dental professionals can now tailor treatments based on individual genetic profiles, enhancing the efficacy of interventions for conditions such as periodontitis, dental caries, and craniofacial anomalies. Additionally, this review discusses the implications of genetic discoveries in developing biomarker-driven diagnostics and the potential of multi-omics research to further understand and combat oral diseases.

Key words: genetic testing; pharmacogenomics; precision dentistry

INTRODUCTION

Integrating genetic insights into dentistry marks a revolutionary shift from traditional treatment approaches to proactive, personalized dental care. With advances in genetic research, dental professionals are now equipped with tools that enable early disease prediction, risk assessment, and targeted therapy. As genomic technologies evolve, they unravel the complex genetic underpinnings of oral diseases, ranging from periodontal disease and dental caries to oral cancer and craniofacial anomalies. By identifying genetic predispositions, clinicians are moving toward a precision approach in dentistry.

GENETIC BASIS OF ORAL DISEASES

Genetic factors play a crucial role in the susceptibility, progression, and therapeutic outcomes of various oral diseases, including periodontitis, dental caries, craniofacial

anomalies, and oral squamous cell carcinoma (OSCC) [1]. Each condition is influenced by distinct genetic variations, such as those affecting inflammatory responses, enamel formation, craniofacial development, and cellular signaling pathways [2,3]. Recent advances in genetic research have significantly deepened our understanding of these diseases' molecular mechanisms, emphasizing the critical interplay between genetic predispositions and environmental factors such as tobacco exposure and oral hygiene [4,5].

The advent of next-generation sequencing (NGS) technologies has revolutionized dental genetics by enabling comprehensive analysis of genetic variations associated with oral diseases [6]. NGS allows for the identification of novel genetic markers, facilitating a deeper understanding of disease mechanisms and genetic

predispositions. These advancements have enhanced our ability to study complex interactions between genetic factors and environmental influences, providing valuable insights into disease pathogenesis [7]. Furthermore, NGS technologies have significantly contributed to identifying potential therapeutic targets and developing biomarker-driven diagnostic tools, paving the way for precision dentistry [8]. By offering high-throughput, cost-effective, and scalable solutions, NGS has become an indispensable tool in advancing research and clinical applications in dental genetics [9].

Periodontitis, a chronic inflammatory disease characterized by the progressive destruction of periodontal tissues, serves as a prime example of this genetic influence [10-12]. Variants in cytokine genes such as Interleukin-1 beta (IL-1 β), Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF- α) have been shown to modulate inflammatory responses, contributing to disease susceptibility and severity. Specifically, polymorphisms like IL-1 β (+3954C>T), IL-6 (-174G>C), and TNF-alpha (-308G>A) are associated with altered cytokine expression profiles, leading to an exaggerated immune response and accelerated tissue destruction [13,14]. These genetic markers not only provide insights into the disease's molecular pathology but also hold promise as biomarkers for early diagnosis and personalized therapeutic interventions [14]. Future multi-omics research will be essential for integrating genetic, transcriptomic, and epigenetic data to fully elucidate the pathogenesis of periodontitis [15]. For example, studies utilizing transcriptomic analysis have revealed distinct gene expression profiles in individuals with aggressive periodontitis, highlighting pathways involved in immune regulation and tissue destruction [16]. Similarly, epigenetic studies have shown

how DNA methylation patterns influence cytokine gene expression, further modulating disease severity [17]. These insights underscore the potential of multi-omics approaches to unravel the complex genetic architecture of periodontitis and guide targeted therapeutic strategies.

Similarly, dental caries represents another multifactorial disease influenced by genetic factors [18]. Variations in enamel formation genes, including AMELX (Amelogenin, X-linked), DSPP (Dentin Sialophosphoprotein), and TUFT1 (Tuftelin), play crucial roles in determining enamel composition, structure, and resistance to demineralization [19]. Mutations in these genes can lead to enamel hypomineralization, increasing vulnerability to cariogenic challenges [19,20]. Additionally, genes associated with saliva composition, such as PRH1 (Proline-Rich Protein HaeIII Subfamily 1) and PRB4 (Proline-Rich Protein BstNI Subfamily 4), influence salivary buffering capacity, protein content, and antimicrobial properties. These variations can weaken the protective function of saliva, further predisposing individuals to dental caries [21]. Understanding these genetic determinants is critical for developing targeted preventive and therapeutic strategies, and future genomic and proteomic research will provide deeper insights into the disease's genetic architecture. For example, a recent genome-wide association study (GWAS) identified specific genetic loci linked to susceptibility to dental caries, shedding light on genes associated with enamel mineralization and salivary composition [22]. Additionally, proteomic analyses have revealed unique protein biomarkers in saliva that could serve as early diagnostic tools for assessing caries risk [23]. These findings highlight the potential of genomic and proteomic research in advancing personalized dental care and improving

preventive strategies.

Craniofacial anomalies, including cleft lip and palate, further illustrate the genetic basis of oral diseases [24]. Mutations and polymorphisms in developmental genes such as MSX1 (Muscle Segment Homeobox 1), FGFR2 (Fibroblast Growth Factor Receptor 2), and PAX9 (Paired Box Gene 9) are strongly associated with craniofacial malformations [24]. These genes regulate key cellular processes, including proliferation, differentiation, and migration, during craniofacial development [26]. Disruptions in these signaling pathways can result in incomplete tissue fusion and abnormal structural formation. Advances in genomic technologies, such as next-generation sequencing and genome-wide association studies (GWAS), have expanded our understanding of these complex pathways, offering potential for improved diagnostics, targeted therapies, and genetic

counseling [27]. Further multi-omics approaches are essential to uncover gene-environment interactions and develop personalized strategies for the prevention and treatment of craniofacial anomalies. However, a significant challenge remains in bridging the gap between identifying genetic variants and understanding their functional impacts on craniofacial development [28]. Limited availability of large, diverse genetic datasets and the complexity of gene-environment interactions further hinder comprehensive analysis. Addressing these challenges will require collaborative, interdisciplinary efforts and advanced bioinformatics tools to unravel the intricate mechanisms underlying craniofacial anomalies. In summary, Table 1 below illustrates the associations between various genetic markers and common oral diseases, detailing their roles and impacts on these conditions.

Table 1. Genetic markers and their associations with oral diseases

Disease	Genetic Marker	Role of Genetic Marker	Impact on Disease
Periodontitis	IL-1 β	Modulates inflammatory responses	Contributes to severity and susceptibility
	IL-6	Involved in immune and inflammatory responses	Influences disease progression
	TNF- α	Regulates inflammation and immune function	Linked to tissue destruction and disease severity
Dental Caries	AMELX	Affects enamel formation	Leads to enamel hypomineralization
	DSPP	Involved in dentin formation	Influences structural integrity of teeth
Craniofacial Anomalies	MSX1	Regulates craniofacial development	Associated with malformations like cleft palate
	FGFR2	Controls cell division, growth, and maturation	Linked to syndromic craniosynostosis
OSCC	TP53	Tumor suppressor, controls cell cycle	Mutations often found in cancerous tissue

IL-1 β : Interleukin-1 beta; IL-6: Interleukin-6; TNF- α : Tumor Necrosis Factor-alpha; AMELX: Amelogenin, X-linked; DSPP: Dentin Sialophosphoprotein; MSX1: Msh Homeobox 1; FGFR2: Fibroblast Growth Factor Receptor 2; OSCC: oral squamous cell carcinoma; TP53: Tumor Protein p53.

GENETIC TESTING IN DENTISTRY

Genetic testing has become an essential tool in dentistry, focusing on translating genetic insights into practical clinical applications that improve patient outcomes.

In disease risk prediction, genetic testing allows clinicians to identify individuals predisposed to conditions such as periodontal disease and dental caries based on well-studied genetic markers like IL-1 β

and AMELX [29]. This enables early intervention strategies, such as proactive oral health monitoring and personalized preventive measures, reducing the likelihood of disease progression. In treatment personalization, genetic markers guide therapeutic decisions, allowing for customized interventions tailored to an individual's unique genetic profile. For example, targeted remineralization therapies can address enamel defects, while anti-inflammatory therapies can manage heightened immune responses in periodontal disease [30]. Additionally, in the context of oral cancer, genetic testing facilitates the early detection of mutations associated with increased cancer risk, enabling timely therapeutic interventions and improved prognosis [31]. Collectively, these clinical applications underscore the transformative impact of genetic testing in dentistry, shifting the focus from reactive to proactive and precision-driven dental care. By analyzing specific genetic markers, such as IL-1 β for cytokine production and AMELX for enamel formation, it is possible to predict susceptibility to diseases like periodontal disease and dental caries [14,32]. These well-studied markers provide valuable insights into individual genetic predispositions, allowing clinicians to implement targeted preventive strategies and reduce disease risk effectively. This predictive capacity allows for early intervention and the implementation of preventive measures tailored to an individual's genetic profile. Unlike traditional preventive strategies, which often rely on generalized recommendations for oral hygiene and routine dental check-ups, genetic testing enables a more personalized approach. For example, individuals identified with genetic predispositions to heightened inflammatory responses can benefit from proactive anti-inflammatory

therapies, while those with markers for enamel defects might receive specialized remineralization treatments before significant damage occurs [33,34]. This targeted approach reduces the likelihood of disease progression and enhances the effectiveness of preventive measures, ultimately offering a higher standard of individualized dental care.

In addition to disease prediction, genetic insights are reshaping treatment personalization. For instance, individuals with genetic markers linked to enamel defects can benefit from targeted remineralization therapies designed to address specific genetic vulnerabilities [35]. Similarly, patients predisposed to heightened inflammatory responses in periodontal disease can receive anti-inflammatory therapies specifically optimized for their genetic makeup, improving treatment outcomes and reducing complications [36]. Both examples illustrate how genetic testing allows clinicians to move beyond generalized treatment protocols, enabling precise interventions tailored to an individual's genetic profile. This approach not only improves treatment efficacy but also minimizes unnecessary interventions, ultimately enhancing overall patient care and outcomes.

Genetic testing has become a pivotal tool in the early detection and management of oral cancer, with clinical applications demonstrating significant advancements in patient care. By leveraging advanced sequencing technologies, clinicians can identify individuals at heightened risk of OSCC through mutations in genes like TP53 and disruptions in pathways such as PI3K-AKT [37]. This knowledge has translated into actionable clinical strategies, including routine genetic screening for at-risk populations, early-stage cancer monitoring, and optimized therapeutic approaches

tailored to genetic profiles. For example, Monteiro et al. have shown that patients identified with high-risk mutations benefit from earlier interventions, resulting in improved survival rates and better treatment outcomes [38]. Additionally, case studies of Cao et al. have highlighted successful implementation of personalized therapies targeting these genetic abnormalities, underscoring the role of genetic testing in bridging the gap between molecular insights and clinical practice [39]. These examples emphasize how genetic testing goes beyond theoretical knowledge, providing concrete benefits in enhancing prognosis, reducing treatment delays, and improving the quality of life for patients undergoing cancer treatment.

PHARMACOGENOMICS IN DENTISTRY

Pharmacogenomics, an evolving field at the intersection of pharmacology and genomics, examines how genetic factors influence an individual's response to drugs [40]. In the realm of dentistry, this discipline is increasingly recognized for its potential to tailor dental care more precisely to each patient's genetic makeup, particularly in areas such as anesthesia and pain management.

Anesthesia Management

In the domain of anesthesia management, pharmacogenomics plays a crucial role by identifying genetic variations that influence the metabolism of local anesthetics, thereby impacting their efficacy and safety. Cytochrome P450 enzymes, particularly CYP1A2 and CYP3A4, are key players in the metabolism of many drugs, including the commonly used local anesthetic lidocaine [41]. Genetic polymorphisms in the CYP genes can lead to varied enzymatic activity among individuals, categorizing them into poor, intermediate, extensive, or ultra-rapid

metabolizers [42]. This variation can significantly affect the plasma concentration of lidocaine during dental procedures.

For instance, a patient who is a poor metabolizer may experience heightened sensitivity to lidocaine, resulting in prolonged anesthesia effects and an increased risk of systemic toxicity [43]. On the other hand, an ultra-rapid metabolizer may require higher or more frequent doses to achieve effective anesthesia [44]. Accurate knowledge of a patient's CYP genotype can guide dentists in adjusting the dosage to optimize anesthesia while minimizing adverse effects [45].

Moreover, beyond CYP1A2 and CYP3A4, other cytochrome P450 enzymes like CYP2A6, CYP2B6, CYP2D6 and CYP2E1 also play roles in drug metabolism that can affect dental treatments [46]. The integration of pharmacogenomic testing into dental practices can lead to more predictable and safer anesthesia management, ensuring that each patient receives a personalized approach to pain control and sedation.

Pain Management

Pain management is another critical area within dentistry where pharmacogenomics can have a transformative impact. Variations in genes related to the opioid pain relief pathway, particularly the OPRM1 gene, which encodes the mu-opioid receptor, have significant implications for the effectiveness and safety of opioid analgesics [47]. These genetic differences can alter the receptor's binding affinity and the patient's overall response to opioids [48].

Patients with certain OPRM1 variants may experience less pain relief from standard doses of opioids, necessitating higher doses for effective pain management [45,48]. Conversely, those with variants that increase receptor sensitivity might be at higher risk for opioid-induced side effects, such as respiratory depression and drug

dependence [48,49]. By identifying these genetic markers, dentists can tailor opioid prescribing practices, opting for non-opioid analgesics or alternative opioids that are better suited to the patient's genetic profile [50].

Additionally, pharmacogenomic insights can also guide the use of non-opioid pain relievers, such as non-steroidal anti-inflammatory drugs and acetaminophen, by identifying genetic markers related to drug metabolism and risk of adverse reactions [51]. This holistic approach not only enhances the effectiveness of pain management strategies but also significantly reduces the risk of side effects and complications associated with inappropriate drug use.

The implementation of these personalized pain management protocols in dentistry represents a paradigm shift towards a more patient-centric approach, where treatment plans are tailored not only to the clinical symptoms but also to the genetic predispositions of each individual, thereby optimizing therapeutic outcomes and patient satisfaction.

The application of pharmacogenomics in dental practice promises several benefits, including enhanced safety profiles of anesthetic and analgesic agents and improved patient outcomes [52]. However, integrating pharmacogenomic data into everyday dental practice requires access to genetic testing and a good understanding of genetic influences on drug metabolism by dental professionals [53].

For effective implementation, dental practitioners need to be trained on the basics of pharmacogenomics and how to interpret genetic testing results [54]. Moreover, dental schools should consider incorporating pharmacogenomics into their curricula to prepare future dentists for this personalized approach to patient care [55].

Despite its potential, the incorporation of pharmacogenomics into clinical dentistry faces several challenges [56]. These include the costs of genetic testing, the complexity of interpreting test results, and the ethical considerations surrounding genetic data. Patients might also have concerns about privacy and the potential misuse of their genetic information [57].

As research continues and technology advances, pharmacogenomics is set to become more accessible and practical for routine use in dentistry [58]. Future developments could lead to more comprehensive genetic panels that provide insights into a broader range of medications beyond anesthetics and painkillers, further personalizing dental care [59]. Additionally, ongoing advancements in bioinformatics and the integration of artificial intelligence could facilitate the interpretation and application of pharmacogenomic data, making it an integral part of precision dentistry [60].

By understanding and embracing the principles of pharmacogenomics, dental professionals can significantly improve the precision of dental medication administration, moving towards a more personalized and effective approach to dental care.

APPLICATIONS OF GENETICS IN PRECISION DENTISTRY

The integration of genetics into dentistry heralds a new era of precision care, where treatments are individually tailored based on genetic profiles. This approach not only improves the efficacy of interventions but also enhances preventive strategies by targeting the genetic underpinnings of dental diseases. Moreover, the incorporation of genomic sciences further signifies a transformative shift towards precision medicine, enabling highly tailored therapeutic interventions that amplify

treatment effectiveness. Figure 1 provides a detailed description of the most important directions for integrating genomic research results into preventive, predictive,

personalized, and participatory dentistry in the 21st century, from targeted caries prevention to innovative regenerative therapies.

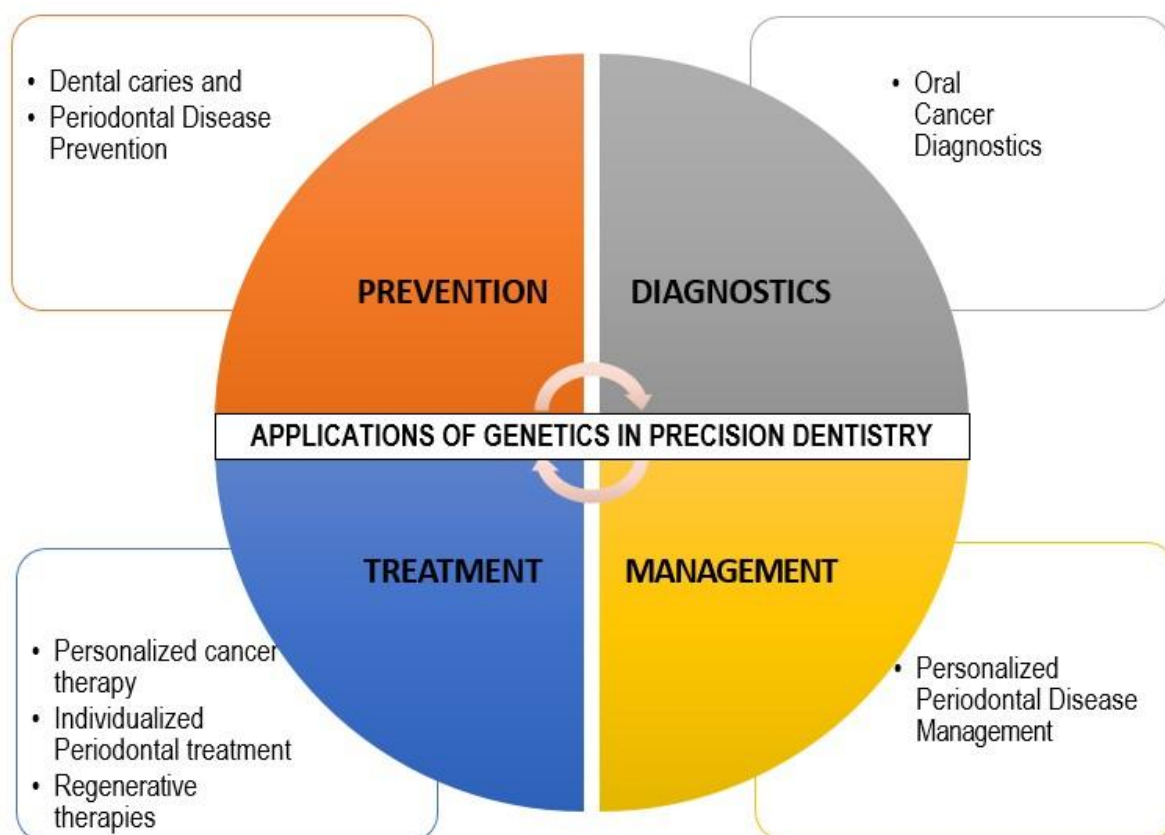


Figure 1. Applications of genetics in precision dentistry

Personalized Caries Prevention

The prevention of dental caries has traditionally employed a one-size-fits-all approach, primarily focusing on fluoride use, oral hygiene, and diet management [61]. However, the advent of genetic testing has allowed for a more nuanced approach by identifying individuals at high risk due to their genetic makeup. Genetic markers associated with enamel formation, such as those in the AMELX (amelogenin) and ENAM (enamelin) genes, can indicate a predisposition to weaker enamel, which is more susceptible to caries [62]. Similarly, variations in the genes related to salivary composition and flow, such as those influencing aquaporins and mucins, can affect saliva's effectiveness in neutralizing

oral acids and clearing food particles [63].

For those with such genetic predispositions, the use of high-fluoride toothpaste can provide enhanced enamel protection by promoting remineralization more effectively than standard fluoride formulations [64]. Additionally, the application of salivary stimulants or the use of artificial saliva products can help mitigate the reduced buffering capacity and antimicrobial protection provided by the patient's natural saliva [65,66]. Dietary recommendations can also be specifically tailored to reduce the intake of fermentable carbohydrates, thereby decreasing the risk of acid attacks that lead to caries [67-69].

Periodontal Disease Management

Periodontal disease is another area where

genetics plays a critical role. Genetic markers associated with inflammatory response, such as variations in the IL-1 and TNF-alpha genes, can predict an individual's susceptibility to periodontitis and the likely severity of the disease [70]. Using genetic risk scores derived from these markers, dentists can categorize patients into different risk categories and tailor their treatment accordingly.

Patients identified with high-risk genetic profiles might require more intensive management strategies [71]. This could include more frequent professional cleanings to control plaque and tartar buildup, which are more likely to cause inflammation in genetically susceptible individuals. Targeted antibiotic therapies can also be customized based on the patient's microbial flora and genetic propensity towards inflammation, ensuring that treatment is both precise and effective [72]. For some high-risk patients, early intervention through surgical means may be necessary to prevent irreversible damage to periodontal tissues.

Oral Cancer Diagnostics

In the realm of oral cancer, genetic biomarkers are increasingly used to enhance early detection and monitoring. The detection of mutations in genes like TP53, which is commonly altered in oral squamous cell carcinoma, can provide early warning signs of cancer development [73]. Liquid biopsy technologies that identify these genetic alterations in blood or saliva are becoming essential tools for non-invasive and ongoing monitoring of patients at risk of oral cancer [74]. Coupled with AI, these technologies analyze genetic and epigenetic data to accurately assess cancer progression or remission, allowing for timely and targeted therapeutic interventions [75].

Regenerative Therapies

Regenerative therapies in dentistry are particularly promising, with gene therapy

and stem cell research at the forefront of enabling actual tissue regeneration. Genetic engineering techniques, including CRISPR-Cas9, offer the potential to directly repair or replace mutated genes responsible for dental anomalies, such as those affecting enamel or dentin formation [76]. This can fundamentally correct the condition at its genetic origin, rather than merely treating its symptoms.

Furthermore, stem cells isolated from dental pulp have shown potential in differentiating into various types of dental tissues [77]. These stem cells can potentially regenerate not only the dentin and enamel but also periodontal structures, offering a holistic regenerative solution for patients suffering from dental and periodontal diseases [78]. This approach could transform treatments for severe conditions that traditionally require extensive surgical interventions, moving towards a more regenerative and restorative strategy.

The incorporation of genetic knowledge into the field of dentistry is transforming it from a predominantly reactive practice to a more proactive and personalized discipline [79]. By understanding and manipulating the genetic basis of dental diseases, the field can advance towards more effective prevention, precise diagnostics, and innovative regenerative therapies [80]. This shift not only promises to improve clinical outcomes but also enhances the quality of life for patients by offering more durable and effective dental care solutions tailored to their genetic profiles.

CONCLUSION

The integration of genetic technologies into dentistry is not just an enhancement of existing practices but a complete overhaul of how oral healthcare is delivered. This paradigm shift towards a genetics-informed approach promises a future where dental

care is not only personalized but also more predictive and preventive. As the field continues to evolve, the synergy between genetic insights and clinical practice will undoubtedly redefine the boundaries of dental medicine, making it more effective, efficient, and tailored to the needs of

individual patients. The ongoing challenge will be to ensure that these advanced genetic tools are accessible and beneficial across diverse populations, ultimately leading to widespread improvements in oral health outcomes.

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