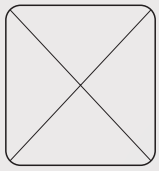
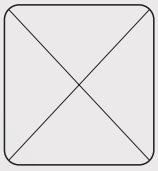
Symposium

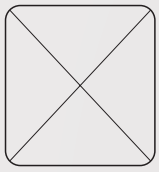
POSI
IJPO



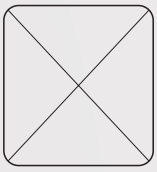
Dr. Neeraj Vij



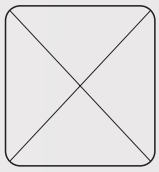
Dr. Jessica Burns



Dr. Melissa Esparza



Dr. Alexandra Dominianni



Dr. Yerin Cho

Dr. Mohan V. Belthur

Address of Correspondence
Dr. Mohan V. Belthur,
Department of Child Health & Orthopaedics, University of Arizona, College of Medicine, Phoenix, Arizona, USA.
Department of Orthopedics, Phoenix Children's Hospital, Phoenix, Arizona, USA.
E-mail: mbelthur@phoenixchildrens.com

[1]Department of Child Health & Orthopaedics, University of Arizona, College of Medicine, Phoenix, Arizona, USA.
[2]Department of Orthopedics, Phoenix Children's Hospital, Phoenix, Arizona, USA.

DOI- 10.13107/ijpo.2022.v08i01.129 | www.ijpoonline.com

Diagnosis of Pediatric Musculoskeletal Infections: Current Concepts Review

Neeraj Vij BS[1], Jessica Burns MD[2], Melissa Esparza Md[2], Alexandra Dominianni BA[1], Yerin Cho BS[1], Mohan V Belthur MD[1,2]

Abstract

Introduction: Paediatric musculoskeletal infections are common and constitute one of the top five conditions contributing to the burden of musculoskeletal disease in childhood. With early accurate diagnosis and appropriate treatment, the clinical course, and outcomes of musculoskeletal infections can be favorable. However, poor outcomes (morbidity/mortality), a wide spectrum of post-infective sequela and significant functional impairment can occur, especially in the setting of delayed diagnosis and inadequate treatment. The purpose of this narrative review is to provide an overview of the standard diagnostic modalities with an emphasis on the recent literature and to summarize the current state of knowledge on the newer diagnostic modalities of the 21st century.

Materials and Methods: A literature search was performed using the following Keywords: "diagnosis", OR "diagnostic modalities", OR "diagnostic capability" AND "children" OR "pediatric" AND "musculoskeletal" OR "bony" OR "orthopedic" OR "muscular" AND "infection" OR "bacterial" OR "viral" OR "fungal". Databases searched included PubMed, EMBASE, Cochrane Library, and SCOPUS. This returned a total of 315 articles. English language articles published between January 1990 and March 2022 regarding traditional or newer diagnostic modalities and pediatric musculoskeletal infection were included in this review.

Results: A total of 62 articles met the inclusion criteria. Our knowledge base regarding the traditional diagnostic modalities has evolved to include several scoring systems with good sensitivities and specificities. Cellular acute phase reactants show promise in the recent literature. There is good literature regarding the evolution of imaging techniques to improve diagnosis. Novel diagnostic modalities in the recent literature include plasma-based acute phase reactants, polymerase chain reaction, and next-generation sequencing.

Conclusion: Continuing to improve our diagnostic accuracy of Pediatric MSKIs can help decrease the worldwide burden of these conditions. As the use of adjunctive biomarkers becomes more common, diagnoses and pathogen identification could be made timelier and antibiotic choices could be individualized leading to improved outcomes. Limited sequence imaging techniques can reduce the associated costs. Polymerase chain reaction and next generation sequencing are important novel technologies that can revolutionize the diagnosis of pediatric musculoskeletal infection.

Keywords: Paediatric, Musculoskeletal Infection, Diagnosis

Introduction

Pediatric musculoskeletal infections (MSKI) are common and constitute one of the top five conditions contributing to the burden of musculoskeletal disease in childhood [1]. With early accurate diagnosis and appropriate treatment, the clinical

Submitted: 29/01/2021; Reviewed: 20/01/2022; Accepted: 28/02/2022; Published: 10/04/2022

course, and outcomes of musculoskeletal infections can be favorable. However, poor outcomes (morbidity/mortality), a wide spectrum of post-infective sequela, and significant functional impairment can occur, especially in the setting of delayed diagnosis and inadequate treatment [2–5].

The physiologic and anatomic considerations of the pediatric musculoskeletal system have many unique considerations that not only play a role in the pathogenesis but also have diagnostic considerations [6]. These include sluggish metaphyseal blood flow and the presence of transphyseal vasculature [5, 6].

Recently, the prevalence of the cytotoxin Panton-Valentine leukocidin (PVL) in methicillin-resistant Staphylococcus aureus (MRSA) infections has increased. There is good evidence to demonstrate that this is related to the increased virulence and pathogenicity of MRSA. This extends across the spectrum of pediatric musculoskeletal infections, including septic arthritis [7], osteomyelitis [8], and pyomyositis [9].

The diagnosis of pediatric musculoskeletal infection is further complicated by the availability of a wide range of diagnostic tests. The clinical utility of newer diagnostic modalities is unknown given the limited knowledge of the psychometric properties. Further, institutional preferences may favor the utilization of certain diagnostic modalities over others.

Recent articles have shed new light on the diagnostic value of traditional diagnostic modalities (laboratory values and imaging studies). Novel diagnostic modalities including biomarkers, polymerase chain reaction (PCR), and next-generation sequencing (NGS) have emerged with the potential to revolutionize the diagnosis of musculoskeletal infections in children. The purpose of this narrative review is to provide an overview of the standard diagnostic modalities with an emphasis on the recent literature and to summarize the current state of knowledge on the newer diagnostic modalities of the 21st century.

Method

A literature search was performed using the following keywords: "diagnosis" [Title/Abstract] OR "diagnostic modalities" [Title/Abstract] OR "diagnostic capability" [Title/Abstract]) AND "children" [Title/Abstract] OR "pediatric" [Title/Abstract]) AND "musculoskeletal" [Title/Abstract] OR "bony" [Title/Abstract] OR "orthopedic" [Title/Abstract] OR "muscular" [Title/Abstract]) AND "infection" [Title/Abstract] OR "bacterial" [Title/Abstract] OR "viral" [Title/Abstract] OR "fungal" [Title/Abstract]). Databases searched included PUBMED, EMBASE, COCHRANE Library, and SCOPUS. This returned a total of 315 articles. All English language articles published between January 1990 and March 2022 regarding traditional or newer diagnostic modalities and pediatric musculoskeletal infection were included.

Results

A total of 62 articles met the inclusion criteria. Our knowledge base regarding the traditional diagnostic modalities has evolved to include several scoring systems with good sensitivities and specificities. Cellular acute phase reactants show promise in the recent literature. There is good literature regarding the evolution of imaging techniques to improve diagnosis. Novel diagnostic modalities in the recent literature include plasma-based acute phase reactants, polymerase chain reaction, and next-generation sequencing.

Discussion

A] Standard Diagnostic Modalities:

Noninvasive methods

Traditional serum markers

Routine laboratory values traditionally utilized in the diagnosis of pediatric MSKI include a complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), C-reaction protein (CRP), and blood cultures. In recent years, there has been much literature regarding the use of additional acute phase reactants (APRs) in the diagnosis of pediatric MSKI.

A recent retrospective review of 265 patients demonstrated that an ESR of ≥ 20 mm/h and a CRP of ≥ 200 mg/L have sensitivities of 94 and 95% for culture-positive osteoarticular infections, respectively [10]. CRP may be the single most important diagnostic marker when working up a patient for suspected pediatric MSKI. Though not very specific, the negative predictive value for CRP is high making it useful to decrease suspicion of an infection in the appropriate clinical setting [11]. Patients with a level of >2.38 mg/dL are 3.5 times as likely to have a musculoskeletal infection [12]. There is strong evidence to suggest its correlation with the risk for deep venous thrombosis development [13] and its value in

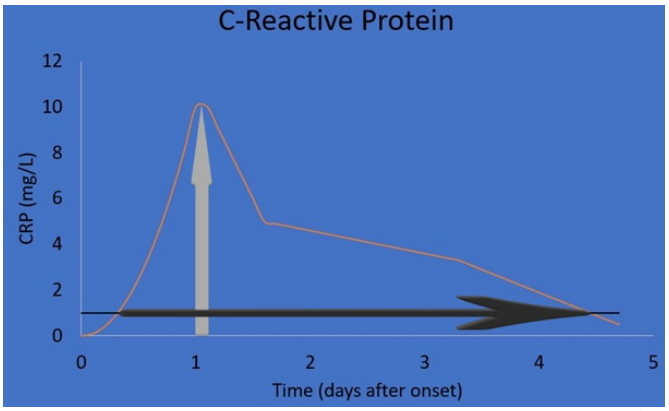


Figure 1: A depiction of an average CRP versus time curve (in orange) in a pediatric patient with MSKI. CRP = 1 mg/L is depicted by the horizontal thin black line. Peak CRP is depicted by the grey vertical arrow, Total CRP is the area under the curve and time to CRP normalization is depicted by the black horizontal arrow.

Table 1: Summary of the use and costs of standard, and novel diagnostic modalities in pediatric musculoskeletal infection. (The costs are estimated prices in the United States for patients within network based on the recent literature.)

Diagnostic Modality	Proposed Use	Cost
C-Reactive Protein	• ≥ 20 mg/L has demonstrated sensitivity of 95% for culture-positive osteoarticular infections.[10]	• $26[71]
	• Peak CRP and trending CRP values play a role in measuring treatment response.[18]	
	• CRP values > 13 mg/L (in addition to other laboratory values) may be useful in distinguishing MRSA and MSSA osteomyelitis.[26]	
Procalcitonin	• Area under the curve of 0.72 for pediatric septic arthritis.[12]	• $26[71]
Complete Blood Count	• Cellular ARP's have a higher psychometric properties than previously thought and may play a large role in early diagnosis	• $16[71]
	• Absolute Neutrophil Count (ANC) and platelet count in particular are useful in determining contiguous infections in cases of septic arthritis.	
	• ANC also plays a role in the prediction of complication of pediatric MSKI's.[16]	
Polymerase Chain Reaction	• High sensitivity (though percentages unreported) for culture-negative *K. Kingae* osteoarticular infection.[55,56]	• $300-2,000[50]
Ultrasound	• Ultrasound serves utility in the diagnosis of pediatric septic arthritis. Ultrasound has great reach in resource-poor settings.	• ~$374[72]
Computed Tomography	• Due to radiation CT is not commonly performed in the diagnosis of pediatric MSKI and is generally not recommended.[6]	• $300-6,750[73]
Magnetic Resonance Imaging	• MRI is currently one of the main resources for diagnosis of pediatric MSKI. T2 sequences are generally thought of as the mainstay, though T1 have good utility for evaluation of the medullar canal.[6]	• $1,055 – $4,775[17]
Target-enriched multiplex polymerase chain reaction (TEM-PCR)	• Theorized improved performance as compared to PCR, however, no studies demonstrate utility in pediatric MSKI.	• Our literature search did not reveal any studies that explored the cost of TEM-PCR.
Cellular Biomarkers	• synovial fluid D-lactate,[46] alpha-defensin[42–44], leukocyte esterase[42], interleukin 16[42], interleukin 18[42], cReLD2[42], neutrophil elastase 2,[44] bactericidal/permeability-increasing protein,[44] neutrophil gelatinase-associated lipocalin,[44] and lactoferrin[44] all demonstrate promise in periprosthetic infections.	• $78[74]
	• However, there are no studies explore the psychometric properties of these in diagnosis of pediatric MSKI.	
Whole Genome Sequencing (WGS)	• Positive predictive value of 93% and negative predictive value of 93% in pediatric osteoarticular infections.[50]	• Pricing may range from $555-$5,169[70]
	• Theorized high sensitivity for PCR-negative infections.[50]	
Whole Exome Sequencing (WES)	• No studies exploring the efficacy of WES in diagnosis of pediatric MSKI	• Pricing may range from $1,906-$24,810[70]

monitoring treatment response [10, 14]. Further, CRP is strongly correlated with disease severity [3, 15, 16]. ESR on the other hand, failed to be included in three of the most recent disease stratification tools, [3, 16, 17] implying that it may have a lower role in the diagnosis of musculoskeletal infections than originally thought.

CRP also has great value in monitoring treatment response [18]. CRP is one of the first acute phase reactants to become elevated in the setting of an infection and can be useful as early as 4-6 hours after the onset of infection. Peak CRP and time to CRP normalization are also important parameters that highlight CRP's utility. Peak CRP is defined as the zenith of the CRP versus time curve (Figure 1). A recent cohort study demonstrated that peak CRP can predict venous thromboembolism with receiver operator curves of 0.90. Further, each 20 mg/L increase in the peak CRP value was correlated with an increased risk of thrombosis by 29% [13]. Higher peak CRP levels have also been associated with contiguous infectious arthritis [19]. Time to CRP normalization is defined as the time to return of the CRP below 1 mg/dL. Time to return of CRP has been associated with failure of medical management, [20] presence of contiguous musculoskeletal infections, [19, 21, 22] multifocal disease, and need for readmission [23, 24] Peak CRP and total CRP both have important value in the diagnosis of pediatric MSKI, monitoring of treatment response, and prediction of adverse outcomes [13, 18].

It is, however, important to note that CRP may be less predictive of osteoarticular infection in the setting of certain pathogens. For example, a level II prospective study of children less than four years revealed a normal CRP on initial presentation in 38% patients of with confirmed Kingella kingae osteoarticular infections [25].

Serum markers can also provide greater insight into the

microbiologic diagnosis than previously thought. For example, MRSA is associated with significantly higher ESR, CRP, and White Blood Count (WBC). A recent retrospective review of 129 patients demonstrated four laboratory-based parameters that can distinguish between MRSA and MSSA infections [26]. The four identified laboratory markers were a temperature of >38°C, a hematocrit value of <34%, a WBC of >12,000 cells/μL, and a CRP level of >13 mg/L. The combination of these four parameters demonstrated a 92% sensitivity in distinguishing these two pathogens [26]. This distinction is an important one that allows clinicians to diagnose and treat MRSA early and aggressively. It may have the potential to reduce the significantly prolonged hospital course [27] and complication rate [28, 29] seen with MRSA musculoskeletal infections.

A few laboratory markers have been found to predict severity and complications for pediatric musculoskeletal infections as well. These include CRP [13, 30], procalcitonin [12, 31], and absolute neutrophil count [16]. Of note to this discussion is the role of procalcitonin (PCT) in the diagnosis of musculoskeletal infections in children. Though traditional literature varies in terms of the reported psychometric properties, there has been recent promise concerning the diagnosis of suspected pediatric septic arthritis. A recent multicenter, prospective study compared the accuracy of the aforementioned traditional biomarkers as compared to PCT. They found an area under the curve (AUC) of 0.72 for PCT, which compared reasonably well to the AUC of CRP (0.88). Though PCT adds significant cost in the workup of suspected septic arthritis, it may have diagnostic value to practitioners faced with suspected septic arthritis [12].

In addition to plasma acute phase reactants, cellular APRs also have an important role in the diagnosis of MSKI. Cellular APRs include neutrophil count, lymphocyte count, platelet count, and neutrophil/lymphocyte ratio [18]. There is literature to suggest that these may have a higher sensitivity and specificity than priorly thought. Particularly neutrophil/lymphocyte ratio has emerged both within pediatric MSKI and other orthopedic infections [32]. Rosenfeld et al. established five parameters that were associated with contiguous MSKI in the setting of pediatric septic arthritis. This included two cellular APR's: platelet count platelet count (< 310 × 10 3 cells/μL) and absolute neutrophil count (> 7.2 × 10 3 cells/μL). Patient age (older than 4 years), duration of symptoms (> 3 days), and C-reactive protein (> 8.9 mg/L) were also associated with MSKI. The presence of >= 3 of these had the following psychometric properties: sensitivity: 90%, specificity: 67%, positive predictive value: 80%, negative predictive value: 83% [30]. This study demonstrates a few important points regarding traditional laboratory values. First, certain traditional laboratory tests, namely CRP, have consistently been shown across multiple studies to have high clinical utility in diagnosing pediatric MSKI. Second, a combination of cellular and plasma APRs should likely be used to maximize sensitivity while minimizing the cost of standard labs (Table 1) [18].

Imaging Studies

Although conventional radiography may not play as large of a role in the diagnosis of musculoskeletal infections, it should still be obtained in cases of suspected infection, given its low cost, availability, and utility in ruling-out other bony lesions. For example, x-rays can be useful in diagnosing oncogenic lesions or pathologic fractures [14]. Radiography is often normal within the first 48 hours to 2 weeks of initial bacterial seeding; however, can demonstrate periosteal reaction and lucencies (acute osteomyelitis); Brodie's abscesses (subacute), round radiolucent areas with sclerotic margins (chronic osteomyelitis); and diaphyseal cystic expansions (tuberculosis osteomyelitis) [6]. Regardless, the sensitivity of radiography alone is low and does allow for potential misdiagnosis as neoplasm or benign reaction.

Magnetic resonance imaging (MRI) is considered an important tool and has the highest sensitivity in the diagnosis of pediatric MSKI. Newer MRI techniques allow for a rapid evaluation of contiguous intra-articular, muscular, and soft tissue infection without the need for sedation. The sequences used vary based on the region of the body scanned, but generally involve a coronal STIR, coronal T1, and an axial T2 fat-saturated sequence [6]. However, there is further potential for the time and costs associated with MRI to improve. Kozak et al. explore the MRI techniques that can be used to improve imaging in children. Rapid-sequence MRI, parallel imaging, and simultaneous multi-section imaging are promising technologies with the potential to reduce imaging times. However, our literature search did not reveal any articles exploring the psychometric properties of rapid-sequence MRI in the diagnosis of pediatric MSK-I [33].

Ultrasound has yet to be incorporated into standardized diagnostic algorithms for pediatric MSKI considering its user-dependent accuracy and variations in institutional preferences. However, given its widespread availability, ultrasound can be very useful. Sonographic findings suggestive of MSKI include deep soft tissue swelling and subperiosteal fluid collection (osteomyelitis); fascial thickening, edema, and gas (necrotizing fasciitis); hypoechoic intramuscular fluid collection (pyomyositis); and joint effusion (septic arthritis) [6]. An anechoic joint effusion can suggest transient synovitis over septic arthritis, among other clinical features [6]. Ultrasound is particularly useful in cases of osteomyelitis with suspicion for contiguous septic arthritis in resource-poor settings where MRI may not be available or there are time constraints that prevent an MRI study.

Invasive methods

Invasive methods to diagnose pediatric MSKI include joint aspirations and bone biopsies. Synovial fluid analysis should always be obtained in cases of suspected Pediatric MSKI that need surgical treatment. However, there is a growing emphasis on obtaining tissue diagnosis in cases of pediatric MSKI that are amenable to non-operative treatment. This is thought to allow for earlier diagnosis, optimization of antibiotic choice based on specific microbiologic diagnoses, and improved hospital course [14]. Traditional wisdom states that in patients without systemic infections, antibiotic administration should be withheld until the appropriate cultures are taken [34]. This is thought to increase bacterial load, increase sensitivity, and allow for a better measure of antibiotic resistance. However, there is recent data to contradict this [18, 35]. A recent retrospective review of 113 patients demonstrated that there was no statistically significant ($p < 0.05$) difference in culture sensitivity after antibiotic administration in both their local and disseminated groups. Further, in the local group only, the authors found that administering antibiotics later was associated with later discharge ($p < 0.05$) [35]. That being said, the most recent guidelines from the Pediatric Infectious Disease Society advised withholding antibiotics for no more than 48-72 hours in patients with Acute hematogenous osteomyelitis (AHO) who are not critically ill [14].

B] Novel diagnostic modalities

Background

Of note to the conversation around the diagnosis of musculoskeletal infections in children are culture-negative infections. Bacterial cultures in general, though a mainstay of the treatment of diagnosis of pediatric MSKI, are inherently limited. These limitations include laboratory processing times, the growing breadth of culture-negative or culture-difficult organisms, significant expenses, and the inability of laboratories to store samples for the adequate periods of time needed for indolent organisms [36].

Culture negative infections have previously been reported as ranging from 30% [37] - 45% [38] in septic arthritis and nearing 52% [39, 40] in acute hematogenous osteomyelitis. However, this may be higher than historically reported. A recent multicenter study found that two out of every three pediatric MSKI are culture negative [41]. These difficult-to-diagnose infections can delay diagnosis and thus treatment. Outside of improvements in culture techniques, novel diagnostic modalities have been developed to address this issue.

Biomarkers

Traditional biomarkers include cellular acute phase reactants that are common additions to the standard laboratory-based workup for musculoskeletal infections [18, 30]. Though they have acceptable sensitivities and good negative predictive values [42–44], there are many clinical scenarios where the use of novel biomarkers is warranted (discussed in section 2.1.1).

Novel biomarkers generally are antimicrobial peptides produced by the body as part of the immune response to a given infection. These include defensins [45], interleukins [42], and other immunogenic peptides [42–44]. Several novel biomarkers have been identified with the potential for improving diagnostic capability. These include synovial fluid D-lactate [46], alpha-defensin [42–44], leukocyte esterase, [42] interleukin 16 [42], interleukin 18 [42], cReLD2 [42], neutrophil elastase 2 [44], bactericidal/permeability-increasing protein [44], neutrophil gelatinase-associated lipocalin,44 and lactoferrin [44]. Of these, alpha-defensin shows the most promise in the current literature in orthopedics.

A recent systematic review demonstrated a high sensitivity of several biomarkers in the diagnosis of periprosthetic joint infection (PJI) [43]. Lee et al. 2017 found that alpha-defensin, leukocyte esterase, and Interleukin 6 and 8 all demonstrated high diagnostic odds ratio's in the diagnosis of PJI [43]. Interleukins 1b and 10 did not demonstrate as high of diagnostic odds ratio though still performed reasonably well. However, the literature is sparse regarding the use of biomarkers in the diagnosis of pediatric MSKI. To date, no studies explore the efficacy, diagnostic potential, psychometric properties, or cost-effectiveness of biomarkers in the use of pediatric MSKI as compared to standard diagnostic studies. This represents a potential area of research, which can further hone clinical suspicion and serve as an intermediate before invasive testing is performed. There is evidence to suggest that adjunctive biomarkers can be meaningfully combined with traditional biomarkers within the world of adult reconstruction [47]. The proper novel biomarkers may have the potential to reduce time to diagnosis, time to surgical intervention, and ultimately reduce the rate of complications following pediatric MSKI. However, this has not been directly explored in the pediatric age group and requires further study.

Polymerase chain reaction (PCR)

Background on polymerase chain reaction

PCR has shown great potential application in the diagnosis of pediatric musculoskeletal infection [25, 48–50]. Polymerase chain reaction utilizes an existing copy of DNA and a heat-resistant polymerase to generate up to tens of billions of copies of a given sequence [51]. Most commonly, the heat-resistant thermophilus aquaticus polymerase is used [52] though others have been described [53]. The process is initiated by denaturing the DNA at high temperatures. Primers of the DNA sequence of interest are placed into the solution, resulting in

elongation and synthesis of the DNA strands.

The utility of polymerase chain reaction in terms of incorporation into existing diagnostic schemes remains unclear. However, PCR does demonstrate great potential in diagnosing multidrug-resistant tuberculosis [54], K. kingae [55–57], distinguishing virulence of MRSA [27, 49], and other difficult to culture organisms [49, 58].

Polymerase chain reaction in difficult to diagnose infections

K. kingae infections are particularly difficult to diagnose and can be culture-negative or slow-growing. This is further complicated by mild or absent symptoms and only minimal elevations in laboratory markers [7]. Further, the incidence of K. kingae in infants [57] and children [59] is increasing. A recent systematic review demonstrated 30.8% confirmed cases in children and 47.8% confirmed cases in children less than four years of age [57]. However, it is important to acknowledge that these statistics do not confirm culture-negative cases for which PCR was not performed or cases for which PCR was inconclusive and thus may represent significant a underrepresentation of the true prevalence of K. kingae infections in children.

Polymerase chain reaction represents a technology with the potential to significantly improve our diagnostic capabilities concerning K. kingae [25, 38, 48]. A recent prospective study studied the diagnostic utility of PCR with the target peptide of Repeats in Toxin (rtxA and rtxB235 loci). The study demonstrated a high detection rate of K. kingae (72.7%) via PCR as compared to the astonishingly low blood and fluid culture rates (9.3% and 7.3%, respectively) [25]. This study also reconfirmed that K. kingae is a predominant cause of septic arthritis in children less than the age of four and that traditional diagnostic measures can fail in this particularly difficult to diagnose bacterium. The conclusion of the authors that PCR may be a useful assay aligns with recommendations in the literature for obtaining specific microbiologic diagnosis before initiation of treatment in stable pediatric patients [14].

Williams et al. 2014 demonstrated very high sensitivity for culture-negative K. kingae pediatric septic arthritis patients. A vast majority of these patients had normal or only slightly elevated WBC, ESR, CRP, and other standard diagnostic modalities. These authors suggested utilizing PCR when all else is negative in these patients [55].

A recent series retrospectively studied [55] patients diagnosed with K. kingae osteoarticular infections [56]. Not a single blood culture was positive, only five synovial fluid cultures were positive, and a large proportion re-presented after initial discharge. This article further highlights the utility of PCR in the diagnosis of K. kingae. It also underscores the need for a standardized pathway that avoids routine PCR due to costs, yet allows for use of PCR in certain, difficult-to-diagnose situations. However, further research is required to better understand the psychometric properties of PCR in these situations, as compared to standard diagnostic modalities as these need to be weighed against the higher costs [60].

Limitations of polymerase chain reaction

There are certain clinical situations where PCR is useful and others where it may not represent a cost-efficient allocation of resources. Drovandi et al. 2018, demonstrated three PCR negative cases of pyomyositis [58]. These patients were diagnosed solely via MRI and treated using a combination of oxacillin, ceftriaxone, or ceftazidime. This study highlights the point, that though the integration of PCR may be an important addition to the diagnosis of certain musculoskeletal infections, it will likely not be used as a catch-all test, and its utility may be higher in certain difficult-to-diagnose infections as compared to others.

An interesting addition to PCR that only recently appeared in the literature is target-enriched multiplex polymerase chain reaction (TEM-PCR) [61]. TEM-PCR allows more focused PCR efforts with better specificity and increased diagnostic potential. A prospective study on 25 children found that TEM-PCR not only provides improved pathogen identification as compared to culture but that TEM-PCR also improves the detection of antibiotic resistance.61 This proof-of-concept study is one of the first to look at the utility of TEM-PCR in the diagnosis of pediatric MSKI and highlights its unique potential.

Next-Generation Sequencing (NGS), Whole Exome Sequencing (WES) & Whole Genome Sequencing (WGS)

NGS has emerged as a potential solution to the limitations of traditional biomarkers and high rates of culture insensitivity in certain pediatric musculoskeletal infections. NGS represents a

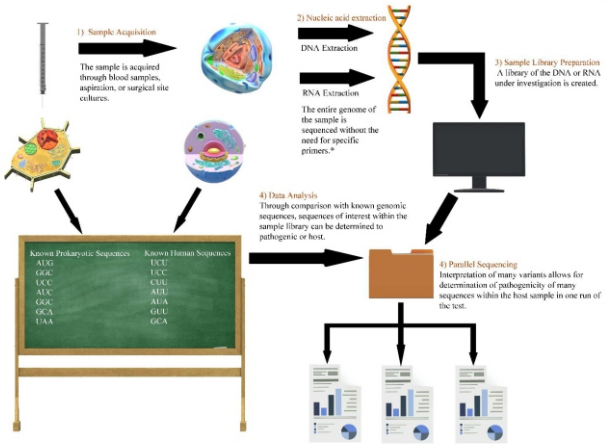


Figure 2: A schematic outlining the process of next generation sequencing.

*The entirety of the genome refers to WGS. In WES, only the exome is translated into the library.

more sophisticated DNA amplification technique that allows for a more comprehensive and organized analysis of the resultant sequences with potential applications in oncology [62, 63], genetic disorders [64], infectious disease [60], and orthopedics [65]. NGS differs from PCR in that it does not rely on the active replication of the DNA being studied. Instead, the entire genome from a given sample can be sequenced [60]. The resultant DNA library can be compared against databases of known human DNA sequences to distinguish between assumed pathogen DNA and host DNA. This gives NGS the potential to revolutionize personalized medicine across specialties [63, 66, 67].

NGS represents a low-cost high-output sequencing method with the potential to revolutionize personalized medicine.68 NGS can rely on both pathogen-specific DNA and RNA sequences, however, has the added capability of parallel sequencing. In other words, NGS can detect thousands of genetic variants in any one given test (Figure 2.) The simultaneous analysis capacity of this technology has the potential to improve efficiency and costs [64].

NGS has demonstrated great potential within the research domain of pediatric musculoskeletal infection. A recent multicenter study studied the role of NGS-specific genotype variants in MSKI. They found good utility in distinguishing between strain genotypes in both pediatric and adult Staphylococcus aureus osteomyelitis. Their murine model also suggested that certain strains have a predisposition for septic arthritis, osteomyelitis, or mixed infections [65]. Other important applications of this technology include better describing the hierarchy of microbiology of pediatric MSKI [69].

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) are targeted variations of NGS that represent a more specific approach to genetic analysis. WES can analyze the entire exome or specific DNA sequences within the exome or an organism [18]. Considering that the exome only represents 1-2% of the human genome, this WES represents a more efficient method that reduces the complexity of library development. WGS, on the other hand, represents the coding of both the exome and intronic regions [68, 70].

The studies exploring the clinical utility of WGS, WES, or NGS are limited. Ramchandar et al [50] demonstrate the clinical utility of NGS in pediatric osteoarticular infections. This single-site prospective study of 42 patients demonstrated high positive and negative predictive values of 93%. However, more noteworthy are the four cases from this study that were both culture and PCR-negative. All four of these cases demonstrated positive NGS testing [50]. Over the breadth of the bacterial spectrum seen in their study, NGS demonstrated good clinical utility. This study not only demonstrates the great potential for NGS in difficult to diagnose cases of pediatric musculoskeletal infection but also demonstrates the need for large prospective studies that compare the efficacy of the newer diagnostic modalities.

NGS cannot be considered without due consideration of its high cost (Table 1.) The cost-effectiveness of a given diagnostic modality is important when considering its integration into diagnostic pathways. Schwarze et al. [70] demonstrated that WES and WGS are significantly more expensive than their traditional diagnostic counterparts ranging from $555-$5,169 and $1,906-$24,810, respectively. These data highlight two important points. Firstly, researchers need to develop more efficient NGS methods that are cost-efficient. Secondly, in clinical practice, focused NGS technologies, such as WES, may have a greater clinical utility when warranted by clinical suspicion of a certain difficult-to-diagnose infection.

Conclusion

The current standard for diagnosis of pediatric musculoskeletal infections includes traditional serum markers and imaging studies. As the use of adjunctive biomarkers becomes more common, diagnoses and pathogen identification could be made more timely and antibiotic choices could be individualized leading to improved outcomes. However, most of the research on novel biomarkers is with regards to adult reconstruction. Significant research is required concerning the use of novel biomarkers in the diagnosis of pediatric musculoskeletal infection.

PCR and NGS are important novel technologies that can revolutionize the diagnosis of pediatric MSKI. However, there are areas for improvement with these technologies that can facilitate their integration into standardized diagnostic pathways. It is known that there is a significant difference in detection rate when PCR is performed using blood samples versus infection site aspirates [25]. A prospective study would be valuable to better evaluate the costs and benefits of using PCR on serum samples versus obtaining infection site aspirates from more invasive methods.

NGS can further improve our ability to diagnose pediatric musculoskeletal infections. The majority of the articles revealed by our literature search demonstrate its use as a research tool as opposed to integration in the clinical setting [65]. WES may represent a more focused approach to NGS that could potentially improve cost-efficacy and specificity; however, further research is needed. Potential areas of improvement include more comprehensive databases, specific amplification processes targeted toward the target bacterium, and improved downstream nucleotide cross-referencing processes. Advancement in these areas could potentially increase the cost-efficacy. Further identification of the particular clinical scenarios in which NGS technologies may be applicable is also required before its integration into routine

clinical practice.

Pediatric MSKIs account for a large burden of disease worldwide, and it is important to continue to improve our diagnostic accuracy and early treatment of these conditions, while also considering cost-effectiveness, resource utilization, and variation in access to some of these newer diagnostic methods. Traditional serum markers and imaging remain a vital aspect in the diagnosis of MSKIs, and more novel biomarkers present an increasingly useful adjunct in optimizing early and accurate diagnosis of these conditions.

Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

References

1. Schwend RM. The Burden of Pediatric Musculoskeletal Diseases Worldwide. Orthop Clin North Am. 2020;51(2). doi:10.1016/j.ocl.2019.11.005.

2. Ilharreborde B. Sequelae of pediatric osteoarticular infection. Orthop Traumatol Surg Res. 2015;101(1). doi:10.1016/j.otsr.2014.07.029.

3. Alhinai Z, Elahi M, Park S, et al. Prediction of Adverse Outcomes in Pediatric Acute Hematogenous Osteomyelitis. Clin Infect Dis. 2020;72(9):454-464. doi:10.1093/cid/ciaa211.

4. Belthur M V., Birchansky SB, Verdugo AA, et al. Pathologic fractures in children with acute Staphylococcus aureus osteomyelitis. J Bone Jt Surg - Ser A. 2012;94(1). doi:10.2106/JBJS.J.01915.

5. Belthur M V., Esparza M, Fernandes JA, Chaudhary MM. Post Infective Deformities: Strategies for Limb Reconstruction. In: Pediatric Musculoskeletal Infections. ; 2022.

6. Furman MS, Restrepo R, Kritsaneepaiboon S, Laya BF, Plut D, Lee EY. Updates and Advances: Pediatric Musculoskeletal Infection Imaging Made Easier for Radiologists and Clinicians. Semin Musculoskelet Radiol. 2021;25(1). doi:10.1055/s-0041-1723004.

7. Arkader A, Brusalis C, Warner WC, Conway JH, Noonan K. Update in Pediatric Musculoskeletal Infections: When It Is, When It Isn't, and What to Do. J Am Acad Orthop Surg. Published online 2016. doi:10.5435/JAAOS-D-15-00714.

8. Funk SS, Copley LAB. Acute Hematogenous Osteomyelitis in Children: Pathogenesis, Diagnosis, and Treatment. Orthop Clin North Am. 2017;48(2):199-208. doi:10.1016/j.ocl.2016.12.007.

9. Vij N, Ranade AS, Kang P, Belthur M V. Primary Bacterial Pyomyositis in Children: A Systematic Review. J Pediatr Orthop. 2021;41(9). doi:10.1097/BPO.0000000000001944.

10. Paakkonen M, Kallio MJT, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. Clin Orthop Relat Res. 2010;468(3). doi:10.1007/s11999-009-0936-1.

11. Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J Pediatr Orthop. 2003;23(3). doi:10.1097/00004694-200305000-00018.

12. McMichael BS, Nickel AJ, Christensen EW, et al. Discriminative Accuracy of Procalcitonin and Traditional Biomarkers in Pediatric Acute Musculoskeletal Infection. Pediatr Emerg Care. 2021;37(12). doi:10.1097/pec.0000000000001978.

13. Amaro E, Marvi TK, Posey SL, et al. C-Reactive protein predicts risk of venous thromboembolism in pediatric musculoskeletal infection. J Pediatr Orthop. 2019;39(1). doi:10.1097/BPO.0000000000001256.

14. Woods CR, Bradley JS, Chatterjee A, et al. Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. J Pediatric Infect Dis Soc. 2021;10(8):801-844. doi:10.1093/jpids/piab027.

15. Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. J Bone Jt Surg - Ser A. 2004;86(8). doi:10.2106/00004623-200408000-00005.

16. Athey AG, Mignemi ME, Gheen WT, Lindsay EA, Jo CH, Copley LA. Validation and Modification of a Severity of Illness Score for Children with Acute Hematogenous Osteomyelitis. J Pediatr Orthop. 2019;39(2):90-97. doi:10.1097/BPO.0000000000000879.

17. Welling BD, Haruno LS, Rosenfeld SB. Validating an algorithm to predict adjacent musculoskeletal infections in pediatric patients with septic arthritis. Clin Orthop Relat Res. 2018;476(1). doi:10.1007/s11999.0000000000000019.

18. Stephanie N. Moore-Lotridge, PhD; Breanne H.Y. Gibson, BS; Matthew T. Duvernay, PhD; Jeffrey E. Martus MD; Isaac P. Thomsen MD, MSCI; Jonathan G. Schoenecker, MD P. Pediatric Musculoskeletal Infection - An Update Through the Four Pillars of Clinical Care and Immunothrombotic Similarities With COVID-19. JPOSNA. 2020;2(2):Online Only. Accessed 09/14/2021.

19. Arnold JC, Cannavino CR, Ross MK, et al. Acute bacterial osteoarticular infections: Eight-year analysis of C-reactive protein for oral step-down therapy. Pediatrics. 2012;130(4). doi:10.1542/peds.2012-0220.

20. Roine I, Faingezicht I, Arguedas A, Herrera JF, Rodríguez F. Serial serum C–reactive protein to monitor recovery from acute hematogenous osteomyelitis in children. Pediatr Infect Dis J. 1995;14(1). doi:10.1097/00006454-199501000-00008.

21. Chou ACC, Mahadev A. The use of c-Reactive protein as a guide for transitioning to oral antibiotics in pediatric osteoarticular infections. J Pediatr Orthop. 2016;36(2). doi:10.1097/BPO.0000000000000427.

22. Kallio MJT, Unkila-Kallio L, Aalto K, Peltola H. Serum C-reactive protein, erythrocyte sedimentation rate and white blood cell count in septic arthritis of children. Pediatr Infect Dis J. 1997;16(4). doi:10.1097/00006454-199704000-00015.

23. Roine I, Arguedas A, Faingezicht I, Rodriguez F. Early detection of sequela-prone osteomyelitis in children with use of simple clinical and

laboratory criteria. Clin Infect Dis. 1997;24(5). doi:10.1093/clinids/24.5.849.

24. Martin AC, Anderson D, Lucey J, et al. Predictors of outcome in pediatric osteomyelitis: Five years experience in a single tertiary center. Pediatr Infect Dis J. 2016;35(4). doi:10.1097/INF.0000000000001031.

25. Ceroni D, Cherkaoui A, Ferey S, Kaelin A, Schrenzel J. Kingella kingae osteoarticular infections in young children: Clinical features and contribution of a new specific real-time PCR assay to the diagnosis. J Pediatr Orthop. 2010;30(3). doi:10.1097/BPO.0b013e3181d4732f.

26. Ju KL, Zurakowski D, Kocher MS. Differentiating between methicillin-resistant and methicillin-sensitive Staphylococcus aureus osteomyelitis in children: An evidence-based clinical prediction algorithm. J Bone Jt Surg - Ser A. 2011;93(18). doi:10.2106/JBJS.J.01154.

27. Martínez-Aguilar G, Avalos-Mishaan A, Hulten K, Hammerman W, Mason EO, Kaplan SL. Community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus musculoskeletal infections in children. Pediatr Infect Dis J. 2004;23(8). doi:10.1097/01.inf.0000133044.79130.2a.

28. Burdette SD, Watkins RR, Wong KK, Mathew SD, Martin DJ, Markert RJ. Staphylococcus aureus pyomyositis compared with non-Staphylococcus aureus pyomyositis. J Infect. 2012;64(5). doi:10.1016/j.jinf.2012.01.005.

29. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: Emergence of community-associated methicillin-resistant Staphylococcus aureus. J Pediatr Orthop. Published online 2006. doi:10.1097/01.bpo.0000242431.91489.b4.

30. Rosenfeld S, Bernstein DT, Daram S, Dawson J, Zhang W. Predicting the presence of adjacent infections in septic arthritis in children. J Pediatr Orthop. 2016;36(1). doi:10.1097/BPO.0000000000000389.

31. Katz SE, Crook J, McHenry R, Szeles A, Halasa N, Banerjee R. Prospective Observational Study to Determine Kinetics of Procalcitonin in Hospitalized Children Receiving Antibiotic Therapy for Non-Critical Acute Bacterial Infections. Infect Dis Ther. 2021;10(1). doi:10.1007/s40121-020-00358-7.

32. Yu BZ, Fu J, Chai W, Hao LB, Chen JY. Neutrophil to lymphocyte ratio as a predictor for diagnosis of early Periprosthetic joint infection. BMC Musculoskelet Disord. 2020;21(1). doi:10.1186/s12891-020-03704-5.

33. Kozak BM, Jaimes C, Kirsch J, Gee MS. Mri techniques to decrease imaging times in children. Radiographics. 2020;40(2). doi:10.1148/rg.2020190112.

34. Copley LAB. Recent advances in the evaluation and treatment of pediatric musculoskeletal infection. Curr Orthop Pract. 2013;24(6). doi:10.1097/BCO.0000000000000037.

35. Benvenuti MA, An TJ, Mignemi ME, Martus JE, Thomsen IP, Schoenecker JG. Effects of Antibiotic Timing on Culture Results and Clinical Outcomes in Pediatric Musculoskeletal Infection. J Pediatr Orthop. 2019;39(3):158-162. doi:10.1097/BPO.0000000000000884.

36. Brolin TJ, Hackett DJ, Abboud JA, Hsu JE, Namdari S. Routine cultures for seemingly aseptic revision shoulder arthroplasty: are they necessary? J Shoulder Elb Surg. 2017;26(11). doi:10.1016/j.jse.2017.07.006.

37. Lyon RM, Evanich JD. Culture-negative septic arthritis in children. J Pediatr Orthop. 1999;19(5). doi:10.1097/01241398-199909000-00020.

38. Ilharreborde B, Bidet P, Lorrot M, et al. New real-time PCR-based method for Kingella kingae DNA detection: Application to samples collected from 89 children with acute arthritis. J Clin Microbiol. 2009;47(6). doi:10.1128/JCM.00144-09.

39. Vij N, Singleton I, Kang P, Esparza M, Burns J, Belthur M V. Clinical Scores Predict Acute and Chronic Complications in Pediatric Osteomyelitis: An External Validation. J Pediatr Orthop. Published online 2022. doi:0.1097/BPO.0000000000002159.

40. Russell CD, Ramaesh R, Kalima P, Murray A, Gaston MS. Microbiological characteristics of acute osteoarticular infections in Children. J Med Microbiol. 2015;64(4). doi:10.1099/jmm.0.000026.

41. Schoenecker JG. Defining the volume of consultations for musculoskeletal infection encountered by pediatric orthopaedic services in the United States. PLoS One. 2020;15(6). doi:10.1371/journal.pone.0234055.

42. Chen MF, Chang CH, Yang LY, et al. Synovial fluid interleukin-16, interleukin-18, and cReLD2 as novel biomarkers of prosthetic joint infections. Bone Jt Res. 2019;8(4). doi:10.1302/2046-3758.84.BJR-2018-0291.R1.

43. Lee YS, Koo KH, Kim HJ, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection : A systematic review and meta-Analysis. J Bone Jt Surg - Am Vol. 2017;99(24). doi:10.2106/JBJS.17.00123.

44. Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing Periprosthetic Joint Infection: Has the Era of the Biomarker Arrived? Clin Orthop Relat Res. 2014;472(11). doi:10.1007/s11999-014-3543-8.

45. Oppenheim JJ, Biragyn A, Kwak LW, Yang D. Roles of antimicrobial peptides such as defensins in innate and adaptive immunity. In: Annals of the Rheumatic Diseases. Vol 62. ; 2003. doi:10.1136/ard.62.suppl_2.ii17.

46. Li Z, Li C, Wang G, et al. Diagnostic accuracy of synovial fluid D-lactate for periprosthetic joint infection: a systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1). doi:10.1186/s13018-021-02778-8.

47. Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid a-defensin and C-reactive protein levels: Highly accurate for diagnosing periprosthetic joint infection. J Bone Jt Surg - Am Vol. 2014;96(17). doi:10.2106/JBJS.M.01316.

48. Al-Qwbani M, Jiang N, Yu B. Kingella kingae-Associated Pediatric Osteoarticular Infections: An Overview of 566 Reported Cases. Clin Pediatr (Phila). 2016;55(14). doi:10.1177/0009922816629620.

49. Gan C, Hu J, Cao Q, et al. Rapid identification of pathogens involved in pediatric osteoarticular infections by multiplex PCR. Ann Transl Med. 2020;8(5). doi:10.21037/atm.2020.01.34.

50. Ramchandar N, Burns J, Coufal NG, et al. Use of Metagenomic Next-Generation Sequencing to Identify Pathogens in Pediatric Osteoarticular Infections. Open Forum Infect Dis. 2021;8(7). doi:10.1093/ofid/ofab346.

51. Kadri K. Polymerase Chaiin Reaction (PCR): Principle and Applications. Intech. Published online 2019.

52. Shah NJ. Polymerase chain reaction. In: Introduction to Basics of Pharmacology and Toxicology: Volume 1: General and Molecular Pharmacology: Principles of Drug Action. ; 2019. doi:10.1007/978-981-32-9779-1_31.

53. Kanno A, Sato T, Mitoma M, Murakami K. A method for sex identification in asparagus using DNA from seeds. Euphytica. 2017;213(9). doi:10.1007/s10681-017-2017-y.

54. Held MFG, Hoppe S, Laubscher M, et al. Epidemiology of musculoskeletal tuberculosis in an area with high disease prevalence. Asian Spine J. 2017;11(3). doi:10.4184/asj.2017.11.3.405.

55. Williams N, Cooper C, Cundy P. Kingella kingae septic arthritis in

children: Recognising an elusive pathogen. J Child Orthop. 2014;8(1). doi:10.1007/s11832-014-0549-4.

56. Awwad E, Tolley M, Antoniou G, Williams N. Clinical presentations of Kingella kingae musculoskeletal infections in South Australian children. J Paediatr Child Health. 2021;57(8). doi:10.1111/jpc.15422.

57. Wong M, Williams N, Cooper C. Systematic Review of Kingella kingae Musculoskeletal Infection in Children: Epidemiology, Impact and Management Strategies . Pediatr Heal Med Ther. 2020;Volume 11. doi:10.2147/phmt.s217475.

58. Drovandi L, Trapani S, Richichi S, Lasagni D, Resti M. Primary Pyomyositis as Unusual Cause of Limp: Three Cases in Immunocompetent Children and Literature Review. J Pediatr Infect Dis. 2018;13(3). doi:10.1055/s-0037-1604036.

59. Juchler C, Spyropoulou V, Wagner N, et al. The Contemporary Bacteriologic Epidemiology of Osteoarticular Infections in Children in Switzerland. J Pediatr. 2018;194. doi:10.1016/j.jpeds.2017.11.025.

60. Ceroni D, Dayer R, Steiger C. Are we approaching the end of pediatric culture-negative osteoarticular infections? Future Microbiol. 2019;14(11). doi:10.2217/fmb-2019-0141.

61. Wood JB, Sesler C, Stalons D, et al. Performance of TEM-PCR vs culture for bacterial identification in pediatric musculoskeletal infections. Open Forum Infect Dis. 2018;5(6). doi:10.1093/ofid/ofy119.

62. Dong L, Wang W, Li A, et al. Clinical Next Generation Sequencing for Precision Medicine in Cancer. Curr Genomics. 2015;16(4). doi:10.2174/1389202915666150511205313.

63. Borate U, Absher D, Erba HP, Pasche B. Potential of whole-genome sequencing for determining risk and personalizing therapy: focus on AML. Expert Rev Anticancer Ther. 2012;12(10). doi:10.1586/era.12.116.

64. Alekseyev YO, Fazeli R, Yang S, et al. A next-generation sequencing primer—how does it work and what can it do? Acad Pathol. 2018;5. doi:10.1177/2374289518766521.

65. Roper PM, Eichelberger KR, Cox L, et al. Contemporary clinical isolates of Staphylococcus aureus from pediatric osteomyelitis patients display unique characteristics in a mouse model of hematogenous osteomyelitis. Infect Immun. 2021;89(10). doi:10.1128/IAI.00180-21.

66. Pasche B, Absher D. Whole-Genome sequencing: A step closer to personalized medicine. JAMA - J Am Med Assoc. 2011;305(15). doi:10.1001/jama.2011.484.

67. Stenson PD, Mort M, Ball E V., Shaw K, Phillips AD, Cooper DN. The Human Gene Mutation Database: Building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. Hum Genet. 2014;133(1). doi:10.1007/s00439-013-1358-4.

68. Michalowitz A, Yang J, Castaneda P, Litrenta J. Existing and emerging methods of diagnosis and monitoring of pediatric musculoskeletal infection. Injury. 2020;51(10). doi:10.1016/j.injury.2020.06.020.

69. Rossen JWA, Friedrich AW, Moran-Gilad J. Practical issues in implementing whole-genome-sequencing in routine diagnostic microbiology. Clin Microbiol Infect. 2018;24(4). doi:10.1016/j.cmi.2017.11.001.

70. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med. 2018;20(10). doi:10.1038/gim.2017.247.

71. Song Z, Lillehaugen T, Wallace J. Out-of-Network Laboratory Test Spending, Utilization, and Prices in the US. JAMA - J Am Med Assoc. 2021;325(16). doi:10.1001/jama.2021.0720.

72. Health H. How much does an ultrasound cost? https://www.honorhealth.com/patients-visitors/average-pricing/ultrasound-costs.

73. New Choice Health. How much does a CT scan cost? https://www.newchoicehealth.com/ct-scan/cost.

74. Vaishya R, Sardana R, Butta H, Mendiratta L. Laboratory diagnosis of Prosthetic Joint Infections: Current concepts and present status. J Clin Orthop Trauma. 2019;10(3). doi:10.1016/j.jcot.2018.10.006.

How to Cite this Article

Vij N, Burns J, Esparza M, Dominianni A, Cho Y, Belthur MV | Diagnosis of Pediatric Musculoskeletal Infections: Current Concepts Review | International Journal of Paediatric Orthopaedics | January-April 2022; 8(1): 14-23.