MSK Genomics England Clinical Interpretation Partnership (GeCIP) Detailed Research Plan Form

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Application Summary	
GeCIP domain name	**Musculoskeletal**
Project title *(max 150 characters)*	**Using Whole Genome sequencing to understand and develop diagnostics and treatments for rare musculoskeletal disorders**

Objectives. *Set out the key objectives of your research. (max 200 words)*

AIM: Improve identification of novel disease genes and modifying factors to inform novel/ repurposing diagnostic testing, accompanying non-invasive biomarkers of disease progression and treatment regimens the NHS using the genomic data.

1. To develop efficient data models for disease nominations within rare musculoskeletal diseases to optimise case finding and clinical data collection.
2. To improve data collection to inform clinical reporting for return to clinicians and patients.
3. To develop a clinical and radiographic ontology for rare musculoskeletal diseases (ultimately to be linked with the HPO) using the RUDY and the dREAMS project respectively. The resulting statistical algorithms will promote more accurate genotype-phenotype correlations. We will also include in the clinical phenotyping a Health Economic component using the RUDY study.

4. To perform research for deeper clinical and molecular phenotyping to improve understanding of the genomic data and optimize development of novel therapies.
5. To signpost opportunities for trainees both within the GeCIP, other GeCIPs and Genomic Education Programmes of Health Education England.

Lay summary. *Information from this summary may be displayed on a public facing website. Provide a brief lay summary of your planned research. (max 200 words)*

There are over 400 rare diseases of the skeleton and for many of them there are no treatments and little understanding of why they happen. The aim of this GeCIP is to use the extensive expertise within the UK to make the most of the information from the 100,000 genomes project so that we can develop better tests and treatments for people with these conditions. We will achieve this by supporting patients with rare bone diseases to get into the project and then, when their results are known, work with them and their doctors so that they can understand the results better. We will study the information from patients (including their symptoms, health care usage and X-ray changes both cross sectionally and longitudinally) to determine sub-phenotypes and link this to their genomic data. This improved scientific understanding will be vital for developing better tests and treatments to improve the care and quality of life of patients. We will study how these new tests and treatments can work for patients in the NHS. Finally, this GeCIP is committed to providing the best training for the next generation of doctors and researchers in rare diseases of the skeleton.

Technical summary. *Information from this summary may be displayed on a public facing website. Please include plans for methodology, including experimental design and expected outputs of the research. (max 500 words)*

This GeCIP will optimize the recruitment of patients with rare bone diseases into the 100,000 Genomes Project by working with doctors across England to increase awareness and with the Genomic Medicine Centres (GMCs) to reduce the burden of recruitment. The GeCIP will then optimize validation, interpretation of variants and enhance training in genomic medicine.

Experimental aims.

1- Deep phenotyping.

We will work with the NIHR RD TRC to refine and/or deep clinical and molecular phenotyping tools to improve our ability to identify sub-phenotypes of rare musculoskeletal diseases both cross sectionally and longitudinally. This will include using dREAMS for radiology and the RUDY study for clinical and health care usage phenotyping both cross sectionally and longitudinally and

2- Interpretation.

After annotation and filtering of sequencing data there will be a significant number of variants with uncertain significance including exonic *de novo* changes, exonic deletions or splice site variants. These variants will require the use and creation of resources for prioritisation such as: developing high quality control variant databases, defining the transcribed portion and regulatory/non-coding regions of the human genome within skeletal tissue, transcriptomic analysis of patient-derived samples and this could contribute to an overarching web resource for variant interpretation across GeCIPs.

3 – Investigation of disease pathways and creation of disease models.

Gene discovery will lead to the identification of novel and/or integration into existing MSK-related diseases pathways that will be investigated and modelled to advance our understanding of disease pathophysiology and mechanisms. Depending on the putative

gene, a wide range of different biochemical, cellular and eventually animal model approaches are available to validate pathogenicity of novel disease genes through collaboration with cross-cutting GeCIPs and in-house.

4 - Development of novel biomarkers and therapeutic agents

We will use the variants with confirmed pathogenicity to identify novel therapeutic targets and develop potential biomarkers for clinical trials.

5 - Evaluation of genomic technologies for the NHS

The development of novel diagnostic (both genomic and non-genomic) and therapeutic interventions has the capacity to transform the NHS. Genomics involves additional sequencing and analytical costs as well as ethical issues, including those around incidental findings. We will work with the existing GECIP in Health economics and Ethics and law to determine these issues within rare bone diseases.

6 – Training.

Genomic medicine is a relatively new area, particularly in rheumatology. We plan to support training of clinical fellows through PhD fellowships, non-clinical PhD studentships, genetic counsellors within associated GMCs, NHS technologists where a higher degree such as an MSc can be taken as part of this training and NHS clinical scientists. This aspect of our research plan will be imperative for the delivery of future benefit to the NHS and public.

Expected start date	**01/09/2017**
Expected end date	**31/05/2022**

Lead Applicant(s)

Name	MK Javaid
Post	Associate Professor in Metabolic Bone Disease
Department	NDORMS
Institution	University of Oxford
Current commercial links	n/a

Deputy Applicant(s)

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Department	Sheffield Diagnostic Genetic Service
Institution	Sheffield Children's NHS Foundation Trust
Current commercial links	n/a

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Subdomain leads		
Name	**Subdomain**	**Institution**
M Irving	Skeletal Dysplasia	Evelina London Children's Hospital, St Guy's and Thomas' NHS Foundation Trust
M Balasubramanian	Bone fragility / Paediatric Metabolic	University of Sheffield
R Keen	Adult Metabolic	University College London Hospitals
A Wilkie	Craniofacial	University of Oxford
D Perry	Orthopaedic	University of Liverpool
R Dalgleish	Analytics	University of Leicester
R Thakker	Functional	University of Oxford
AC Offiah	Imaging/ dREAMS	University of Sheffield
J Kaye	Ethics	University of Oxford
R Pinedo-Villanueva	Health Economics	University of Oxford
C Gregson	Training	University of Bristol
M Wright	Validation	University of Newcastle
M Briggs	Multiple Epiphyseal Dysplasia	University of Newcastle
E Aslin	Patient representative	Patient representative

Detailed research plan

Craniosynostosis

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	Craniosynostosis

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

Craniosynostosis (premature fusion of one or more cranial sutures) is the second most common craniofacial malformation, with a birth prevalence of ~1 in 2250. It is important to recognise and treat because it can be associated with many complications affecting sensory, respiratory and neurological function. Given these challenges, multi-disciplinary assessment and treatment is currently concentrated at four specialist units within England, which are based at Birmingham, Liverpool, London (Great Ormond Street) and Oxford. Between them, these units treat 300-400 new children per year. Additional expertise is available from NHS molecular diagnostic laboratories as genetic diagnostics are offered at just two centres (Great Ormond Street – Alison Taylor-Beadling; Oxford – Tracy Lester and Helen Lord).

Craniosynostosis is heterogeneous in its causes, with monogenic, polygenic, and environmental (mostly prenatal) factors all playing a role. The importance of monogenic causes is illustrated by the fact that a specific mutation or causative chromosomal rearrangement can currently be identified in ~25% of all craniosynostosis. Such monogenic forms are enriched in patients exhibiting a positive family history, additional syndromic features, and fusion of the coronal or

multiple cranial sutures. Overall there are 10-15% of patients who match these characteristics, but in whom a genetic cause cannot currently be identified: GEL sequencing efforts will be focussed on this patient cohort (theoretical maximum ~50 patients/year).

The Oxford WIMM Clinical Genetics Group led by Prof Andrew Wilkie has an internationally leading track record in the application of next generation sequencing (both whole exome and whole genome) to craniosynostosis. They have discovered and published 6 new recurrently mutated disease genes, more than any other group worldwide; several additional genes are currently unpublished (e.g. Sharma *et al*., 2013; Twigg *et al*., 2013; Taylor *et al*., 2015; Twigg *et al*., 2015). Hence they have demonstrated the ability to handle, and make use of, genome-scale data. However, although 44 of the 115 probands/families that they have investigated using these methods are now considered "solved" (38%), the remainder either have candidate genes requiring further evidence, or are unsolved.

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

The Consultant Clinical Geneticists based at the Craniofacial Units listed above (Jenny Morton, Birmingham; Astrid Weber and Emma McCann, Liverpool; Louise Wilson, Great Ormond Street; Deirdre Cilliers and Andrew Wilkie, Oxford) have actively collaborated for the past 6 years to recruit patients for genetic investigations (*Genetics of craniofacial malformations* study). This recruitment will continue within the GEL programme.

Most craniosynostosis occurs sporadically, so the standard GEL trio model is the most suitable for recruitment and analysis. Mutations in over 50 genes are known to be associated with craniosynostosis (Twigg and Wilkie, 2015) and these genes have been curated as part of the PanelApp; we expect information on variants present in these genes to be available from core GEL analyses. Clinical and Molecular Diagnostic GECIP members listed above will be qualified to assist in interpreting the clinical significance of these variants.

If these analyses prove negative, we will widen assessment to the genome scale. As raw material to inform these analyses, we expect to have access to BAM and VCF files and summary data on SNPs, small indels and copy-number variant analyses. These will be interrogated under standard models for mutational origin in sporadic cases (*de novo*, homozygous, compound heterozygous, X-linked recessive). Genes showing *de novo* mutation and other very rare variant combinations will be interrogated against prioritised variants based on multiple criteria including presence in other craniosynostosis patients from our existing cohort.

Strong candidate variants will be evaluated further by a combination of resequencing and functional analysis. Resequencing in large patient DNA panels represents an essential step to establishing causal association, disease prevalence, and genotype-phenotype correlations. For resequencing we have access to over 500 DNA samples from individuals with craniosynostosis who currently lack a genetic diagnosis. In the first instance, functional analyses are likely to involve simple measures to check defective splicing, nonsense-mediated decay, *etc.* Genes mutated in craniosynostosis affect a large number of different signalling pathways and processes including RAS-MAPkinase, hedgehog signalling, retinoic acid, DNA replication and IL11-STAT3 signalling (Twigg and Wilkie, 2015). Craniosynostosis can also represent a low-frequency complication of many disorders. Based on the initial results of the resequencing and functional analyses we will assess the robustness of the causal association with craniosynostosis and, if judged strong and biologically interesting, we have the capacity to explore this further in appropriate mouse models (either off-the-shelf or created by CRISPR-Cas9 genome editing).

Collaborations including with other GeCIPs. *Outline your major planned academic, healthcare, patient and industrial collaborations. This should include collaborations and data sharing with other GeCIPs. Please attach letters of support.*

Paediatric, Ethics, validation,
At this early stage we have not arranged formal collaboration with any other GeCIP, as we anticipate that the majority of patients with craniosynostosis will be recruited and analysed in the current GeCIP.

Training. *Describe the planned involvement of trainees in the research and any specific training that will form part of your plan.*

The Weatherall Institute of Molecular Medicine (WIMM) Clinical Genetics Group currently includes one DPhil student making direct use of next generation sequencing data, with the capacity to extend this further. The Group hosts undergraduate students both from Oxford and elsewhere to undertake short-term projects analysing currently available next-generation sequencing (NGS) data. It has close links to the Oxford NIHR BRC which coordinates NGS analysis activities within Oxford. Further opportunities for training will be available to other GeCIP members if required.

People and track record. *Explain why the group is well qualified to do this research, how the investigators would work together.*
The team will be led by Prof Andrew Wilkie, Nuffield Professor of Pathology at University of Oxford and Honorary Consultant in Clinical Genetics and Dr Steve Twigg, a WIMM Senior Research Fellow who has been working with Prof Wilkie for the past 20 years. These individuals have an internationally leading track record in NGS-based analysis of craniosynostosis. The team has strong bioinformatics support both within the group (Dr Nils Kölling, postdoctoral bioinformatician, who will be available to work half-time on this project) and within the WIMM (Dr Simon McGowan, Computational Biology Research Group, who has been involved in analysis of exome and genome data since 2010). Additional laboratory support from 1 postdoctoral and 1 predoctoral scientist is available (work is funded by the Wellcome Trust and Oxford NIHR BRC).

Clinical interpretation. *(Where relevant to your GeCIP) Describe your plans to ensure patient benefit through clinical interpretation relevant to your domain. This should specifically address variant interpretation and feedback and your interaction with the cross-cutting Validation and Feedback domain.*

As described above, Prof Wilkie has active clinical contact both with consultant geneticists at the other craniofacial units, and with the molecular diagnostic laboratories. Clinical interpretation will be provided by a Working Group comprising key individuals listed above (Cilliers, Differ, Lester, Lord, Morton, Weber, Wilkie and Wilson). Variants passing triage will be validated in either the Great Ormond Street or Oxford laboratories and formal reports issued.

Beneficiaries. *How will the research benefit patients and healthcare institutions including the NHS, other researchers in the field? Are there other likely beneficiaries?*

Patients and their families benefit from accurate diagnosis, explaining their clinical condition and providing information on potential complications, prognosis, and correctly informed genetic counselling. Within the clinic the surgeons can use the genetic diagnosis to guide frequency of clinical monitoring, alert for specific complications and contribute to information on prognosis. The availability of precise molecular diagnosis enables preimplantation or prenatal diagnosis when requested by individuals at risk.

Commercial exploitation. *(Where relevant to your GeCIP) Genomics England has a very explicit intellectual property policy. We and other funders need to know if the proposed research likely to generate commercially exploitable results. Do you have commercial partners in place?*

We do not have any commercial partners at present.

References. *Provide key references related to the research you set out.* (Individuals referred to above are shown in **bold; ***corresponding author)

Sharma VP, Fenwick AL, Brockop MS, **McGowan SJ**, Goos JAC, Hoogeboom AJM, Brady AF, Jeelani NuO, Lynch SA, Mulliken JB, Murray DJ, Phipps JM, Sweeney E, Tomkins SE, **Wilson LC**, Bennett S, Cornall RJ, Broxholme J, Kanapin A, WGS500, Johnson D, Wall SA, van der Spek PJ, Mathijssen IMJ, Maxson RE, **Twigg SRF** & **Wilkie AOM*** (2013). Mutations of *TCF12*, encoding a basic-helix-loop-helix partner of TWIST1, are a frequent cause of coronal craniosynostosis. *Nature Genet* **45**:304-307.

Twigg SRF, Vorgia E, **McGowan SJ**, Peraki I, Fenwick AL, Sharma VP, Allegra M, Zaragkoulias A, Akha ES, Knight SJL, **Lord H**, **Lester T**, Izatt L, Lampe AK, Mohammed SN, Stewart FJ, Verloes A, **Wilson LC**, Healy C, Sharpe PT, Hammond P, Hughes J, Taylor S, Johnson D, Wall SA, Mavrothalassitis G & **Wilkie AOM*** (2013). Reduced dosage of ERF causes complex craniosynostosis in humans and mice, and links ERK1/2 signalling to regulation of osteogenesis. *Nature Genet* **45**:308-313.

Taylor JC, Martin HC, Lise S, Broxholme J, Cazier J-B, Rimmer A, Kanapin A, Lunter G, Fiddy S, Allan C, Aricescu AR, Attar M, Babbs C, Becq J, Beeson D, Bento C, Bignell P, Blair E, Buckle VJ, Bull K, Cais O, Cario H, Chapel H, Copley RR, Cornall R, Craft J, Dahan K, Davenport EE, Dendrou C, Devuyst O, Fenwick AL, Flint J, Fugger L, Gilbert RD, Goriely A, Green A, Greger IH, Grocock R, Gruszczyk AV, Hastings R, Hatton E, Higgs D, Hill A, Holmes C, Howard M, Hughes L, Humburg P, Johnson D, Karpe F, Kingsbury Z, Kini U, Knight J, Krohn J, Lamble S, Langman C, Lonie L, Luck J, McCarthy D, **McGowan SJ**, McMullin MF, Miller KA, Murray L, Németh AH, Nesbit MA, Nutt D, Ormondroyd E, Oturai AB, Pagnamenta A, Patel SY, Percy M, Petousi N, Piazza P, Piret SE, Polanco G, Popitsch N, Powrie F, Pugh C, Quek L, Robbins PA, Robson K, Russo A, Sahgal N, van Schouwenburg PA, Schuh A, Silverman E, Simmons A, Sørensen PS, Sweeney E, Thakker RV, Tomlinson I, Trebes A, **Twigg SRF**, Uhlig H, Vyas P, Vyse T, Wall SA, Watkins H, Whyte MP, Witty L, Wright B, Yau C, Buck D, Humphray S, Ratcliffe PJ, Bell JI, **Wilkie AOM**, Bentley D, Donnelly P & McVean G. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. *Nature Genet* **47**:717-726.

Twigg SRF, Forecki J, Goos JAC, Richardson ICA, Hoogeboom AJM, Van den Ouweland AMW, Swagemakers SMA, Lequin MH, Van Antwerp D, McGowan SJ, Westbury I, Miller KA, Wall SA, WGS500 Consortium, van der Spek PJ, Mathijssen IMJ, Pauws E, Merzdorf CS & Wilkie AOM* (2015). Gain-of-function mutations in *ZIC1* are associated with coronal craniosynostosis and learning disability. *Am J Hum Genet* **97**:378-388.

Twigg, SRF & **Wilkie AOM** (2015). A genetic-pathophysiological framework for craniosynostosis. *Am J Hum Genet* **97**:359-77.

Multiple epiphyseal dysplasia (MED)

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	Multiple epiphyseal dysplasia (MED)

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

Multiple ephiphyseal dysplasia (MED) is one of the more common bone dysplasias affecting ~1 in 20,000 children. Both autosomal dominant and recessive forms are recognised. AD-MED is genetically heterogeneous and results from mutations in the genes encoding matrilin-3, type IX collagen and COMP. However, extensive genetic analysis has consistently demonstrated that mutations in other, as yet unidentified genes, can also result in AD-MED. The proportion of AD-MED that does not have a genetic basis ascribed varies between 30-70% depending on diagnostic rigour. This sub-group of MED patients have been targeted for recruitment to GEL.

Previous studies have also identified cohorts of patients that are phenotypic outliers of the MED 'disease spectrum', but which shared distinct clinical and/or radiographic features. Consensus diagnoses for these patients focuses around specific forms of familial hip dysplasia (FHD) and it is clear that these diseases are genetically distinct from 'classical' forms of MED result from mutation in matrilin-3, type IX collagen and COMP.

Cell and animal studies have consistently shown that in genetically defined AD-MED a core disease mechanism is endoplasmic reticulum (ER) stress due to misfolding of the mutant proteins. ER stress is being increasingly recognized as a common disease mechanism in a range of different human connective tissue diseases and is an attractive target for pharmacological intervention by modulating the cellular response to the expression of mutant proteins, and/or by using chemical chaperones to aid protein folding and/or protein quality control pathways. Indeed, we have recently filed a UK priority patent for the repurposing of carbamazepine (cbz: an inducer of protein degradation) in the treatment of human connective tissue disease (P030925GB) and have filed orphan drug designation with the European Medicines Agency for the use of cbz in metaphyseal chondrodysplasia type Schmid (UPI: 997570).

Identification of the genetic basis of the remaining ~30% of MED will allow disease mechanisms to be defined and therapeutic targets to be investigated including the role of ER stress. Our research strategy will eventually use relevant cellular and animal models for functional validation of genetic variants and in determining molecular mechanisms that underpin disease pathophysiology so that new and validated therapeutic targets can be discovered. This approach will also provide new routes to identify novel biomarkers, which will enable the efficacy of treatment to be monitored and patient subsets to be recognised, thereby leading to personalised treatments and care strategies ('stratified medicine').

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

GEL Data will be compared with candidate genes/variants identified through our in-house exome studies, which encompasses a group of MED patients in which all known disease genes have been previously excluded. Prioritised candidate genes/variants will be functionally validated using cell and mouse models. All relevant expertise is available within the GeCIP consortium.

We will derive iPS cells from patients with MED and differentiate these into relevant cell types such as chondrocytes and determine cellular pathology. If several variants have been identified and prioritised following bioinformatics analysis we will use genome editing (CRISPR/CAS9) to

systematically correct variants and monitor cellular pathology readouts (proliferation rates, apoptosis etc.). These cell models will also act as pre-clinical models for drug screening/repurposing.
The gold standard for disease modelling in skeletal dysplasias is a genetically targeted mouse model and we will use genome editing to generate relevant mouse models for in depth analysis in vivo.
Genome editing and iPS cell technology is available in-house.
There is marked phenotypic variability of patients with MED. We will compare the genotype / phenotype correlation in patients with mutations. This will require developing a detailed phenotyping template within an existing NIHR TRC RD project (RudyStudy.org) we will recruit patients to who have been submitted to GEL. The Rudy study will allow collection of both cross-sectional and longitudinal outcomes data including patient reported outcomes measures of quality of life, health care usage and fracture events.

Collaborations including with other GeCIPs. *Outline your major planned academic, healthcare, patient and industrial collaborations. This should include collaborations and data sharing with other GeCIPs. Please attach letters of support.*

Training. *Describe the planned involvement of trainees in the research and any specific training that will form part of your plan.*

Newcastle delivers an MSc in Genomic Medicine and we have strong links with this taught course by providing tutorials, lectures and final project opportunities.
Currently three full time PhD students and several MSc/BSc students in Newcastle participate in skeletal genetic research. Moreover, research in Newcastle are closely linked with several EU networks that provide additional training programmes (SYBIL until 09/18 and Rubicon until 01/19)

People and track record. *Explain why the group is well qualified to do this research, how the investigators would work together.*
The team will be led by Professor Michael D Briggs, Professor of Skeletal Genetics at Newcastle University and supported closely by Dr Michael J Wright Consultant Clinical Geneticist, Northern Genetic Service. MDB has over 25 years' experience in studying the molecular genetics and disease mechanisms of MED and related conditions. MJW and other members of GeCIP have extensive experience in the clinical and radiographic diagnosis of MED and the various phenotypic outliers.

Clinical interpretation. *(Where relevant to your GeCIP) Describe your plans to ensure patient benefit through clinical interpretation relevant to your domain. This should specifically address variant interpretation and feedback and your interaction with the cross-cutting Validation and Feedback domain.*

Beneficiaries. *How will the research benefit patients and healthcare institutions including the NHS, other researchers in the field? Are there other likely beneficiaries?*

The main beneficiaries of the project are patients and their families by receiving an accurate diagnosis, an explanation for their clinical phenotype, information on potential complications, prognosis, and appropriate genetic counselling. Early diagnosis and institution of appropriate therapies is crucial in this group ensuring better quality of life.

Families will benefit from information on recurrence risks for future pregnancies, allowing informed choices and option of prenatal genetic testing/preimplantation genetic diagnosis.

Clinicians: In addition to patients, clinicians all over will benefit from earlier and more effective methods to diagnose and treat this condition, thanks to the advancement of clinical and scientific knowledge.

Patient support groups: There is no bespoke patient group for MED at present and support is provided by a very active Facebook group and the Perthes Association. We have engagement already with the Facebook group and will develop them further as this project progresses.

Public: It is important to ensure that this proposal has an impact on the wider public locally and beyond. One outcome from this proposal would be better insights into collagen processing. Hence, principles learnt from such research can be applied more broadly to degenerative osteoarthritis which has a large disease burden in the adult population.

Commercial exploitation. *(Where relevant to your GeCIP) Genomics England has a very explicit intellectual property policy. We and other funders need to know if the proposed research likely to generate commercially exploitable results. Do you have commercial partners in place?*

References. *Provide key references related to the research you set out.* (Individual referred to above are shown in **bold; ***corresponding author)

Bone Fragility

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	Bone Fragility

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

Osteogenesis Imperfecta (OI) is the commonest form of inherited bone fragility disorders affecting 1 in 20,000 live births. It is a heterogeneous disease resulting in variable presentations. Dominantly inherited forms of OI are considered to be type 1 collagenopathies, with 90% of patients having mutations in *COL1A1/COL1A2*. In the remainder 10% of patients, a small proportion is due to rare, recessive genes whilst the rest are unknown. It is this group of patients that we are targeting through recruitment to the 100,000 Genomes project and GEL sequencing efforts will be focussed on this patient cohort (10 patients/ year).

Most patients suffer from variable degree of fractures, bone pain and short stature. OI is one such rare genetic condition where treatment is available in the form of bisphosphonates that improve quality of life. Hence, it is important to recognise and treat this condition early as in addition to fractures, it can be associated with impaired mobility, hearing and neurological function if associated complications are not recognised and dealt with early. Given these challenges, multi-disciplinary assessment and treatment is currently concentrated at four specialist units within

England, which are based at Sheffield, Bristol, Birmingham, and London (Great Ormond Street). Between them, these units treat approximately 250 children per year. Additional expertise is available from NHS molecular diagnostic laboratory, since targeted OI exome testing is only offered at Sheffield Diagnostic Genetics Laboratory.

The Bone Genetics group in Sheffield led by Dr Meena Balasubramanian (Bone Fragility subdomain lead) is concentrating efforts on identifying novel causes of bone fragility through in-house exome sequencing studies which has resulted in candidate genes that need further exploration. In addition, this sub-domain benefits from the combined expertise of adult and paediatric metabolic bone clinicians who specialise in looking after patients with OI and personnel from the Sheffield Diagnostic laboratory (R Pollitt) and analytics (Prof R Dalgleish, curator of the OI Variant Database, University of Leicester) within the Bone fragility sub-domain under MSK GeCIP. Hence, we have accumulated a critical mass of personnel which combined with the experience in sequencing studies will help deliver the proposed research plan.

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

The Consultant Clinicians at the specialist centres listed above (Dr Nick Shaw and Dr Wolfgang Hogler, Birmingham; Dr Catherine De Vile, London, Dr Christine Burren, Dr Sarah Smithson, Bristol and Prof Nick Bishop, Dr Paul Arundel and Dr Meena Balasubramanian, Sheffield) have actively collaborated over the last 4 years as part of the 'Highly specialised severe, complex and atypical OI service' and been undertaking genetic analyses as part of diagnostic and research testing for genetic investigations (*Identifying novel causes of bone fragility study*). This recruitment will continue within the GEL programme.

Most unresolved OI are simplex cases with no family history, hence the standard GEL trio model is the most suitable for recruitment and analysis. Mutations in around 20 genes are known to be associated with OI so far (Balasubramanian et al., 2016) and these genes have been curated by this team as part of the PanelApp; we expect information on variants present in these genes to be available from core GEL analyses. Clinical and Molecular Diagnostic GeCIP members listed above will be qualified to assist in interpreting the clinical significance of these variants.

If these analyses prove negative, we will widen assessment to the genome scale. As raw material to inform these analyses, we expect to have access to BAM and VCF files and summary data on SNPs, small indels and copy-number variant analyses. We will use a web-based utility (vcf2hgvs) which automates the conversion of VCF variant calls into HGVS nomenclature-compliant variant descriptions. These will be interrogated under standard models for mutational origin in sporadic cases (*de novo*, homozygous, compound heterozygous, X-linked recessive). Genes showing *de novo* mutation and other very rare variant combinations will be analysed against prioritised variants based on multiple criteria including presence in other OI patients from our existing cohort.

Data will be compared with candidates identified from our in-house exome studies which are an enriched group and these candidates will be further explored by cell and animal (zebrafish model) based studies (through ongoing collaborations with colleagues in Centre for Membrane Interaction and Dynamics and Bateson Centre, University of Sheffield).

There is marked phenotypic variability of patients with OI. We will compare the genotype / phenotype correlation in patients with COL1A1/2 mutations and other recognized but less

common mutations. This will require developing a detailed phenotyping template within an existing NIHR TRC RD project (RudyStudy.org) we will recruit patients to who have been submitted to GEL. The Rudy study will allow collection of both cross-sectional and longitudinal outcomes data including patient reported outcomes measures of quality of life, health care usage and fracture events.

Collaborations including with other GeCIPs. *Outline your major planned academic, healthcare, patient and industrial collaborations. This should include collaborations and data sharing with other GeCIPs. Please attach letters of support.*

Paediatric, Ethics, validation,
At this early stage we have not arranged formal collaboration with any other GeCIP, as we anticipate that the majority of patients with OI will be recruited and analysed in the current GeCIP.

Training. *Describe the planned involvement of trainees in the research and any specific training that will form part of your plan.*

Sheffield hosts the MSc for Genomic Medicine (under the auspices of HEE and led by Prof Win Hide and Dr Janine Kirby). We have strong links with this MSc and provide tutorials and lectures for this course. Dr Meena Balasubramanian has already received approval for a research project to analyse exome data for an MSc student (Dr Akilapa). Further opportunities for training will be available to other GeCIP members if required. As part of ongoing exome studies in Sheffield, Dr Balasubramanian is supervising a BMedSci student making direct use of next generation sequencing data. Through ongoing links with the University of Sheffield, we are also able to undertake short-term projects analysing currently available next-generation sequencing (NGS) data. There are several opportunities available through the Sheffield Diagnostic Genetics Laboratory which undertakes diagnostic next generation sequencing for OI to train lab personnel and scientist trainees (MSc/ PhD students). Other programmes are in development (e.g. University of Leicester).

People and track record. *Explain why the group is well qualified to do this research, how the investigators would work together.*

The team will be led by Dr Meena Balasubramanian, Consultant Clinical Geneticist and Honorary Senior Lecturer at University of Sheffield. There is a strong group of clinicians, lab personnel and analytical expertise available in this group which this research plan will make full use of. Within Sheffield, the core team (Dr M Balasubramanian and R Pollitt) have identified a network of collaborators that will work together on this research plan in addition to working with other members of the GeCIP team.

Clinical interpretation. *(Where relevant to your GeCIP) Describe your plans to ensure patient benefit through clinical interpretation relevant to your domain. This should specifically address variant interpretation and feedback and your interaction with the cross-cutting Validation and Feedback domain.*

Through active clinical contact with metabolic bone clinicians and geneticists from other centres and the Sheffield Diagnostic Genetics Laboratory, variant interpretation will be provided as described above by Dr Meena Balasubramanian. Given the combined expertise within the team, we will ensure that any feedback provided is clinically relevant and involves input from key personnel listed above. Variants considered disease-causing will be validated in the Sheffield

Diagnostic Genetics Laboratory and formal reports issued.

Beneficiaries. *How will the research benefit patients and healthcare institutions including the NHS, other researchers in the field? Are there other likely beneficiaries?*

The main beneficiaries of the project are patients and their families by receiving an accurate diagnosis, an explanation for their clinical phenotype, information on potential complications, prognosis, and appropriate genetic counselling. Early diagnosis and institution of appropriate therapies is crucial in this group ensuring better quality of life.

Families will benefit from information on recurrence risks for future pregnancies, allowing informed choices and option of prenatal genetic testing / preimplantation genetic diagnosis.

Clinicians: In addition to patients, clinicians all over will benefit from earlier and more effective methods to diagnose and treat this condition, thanks to the advancement of clinical and scientific knowledge. This study would benefit the local clinicians and other national OI centres (Birmingham/Bristol and London), as well as specialist paediatric centres.

Patient support groups: This sub-domain works closely with Brittle Bone Society which provides support to patients and families with OI and Unique which deals with children with rare genetic conditions. The outputs of this work will not only inform novel genetic mutations but the genotype/phenotype work is fundamental to informing expected severity and progression for patients and clinicians. This information may identify patients at higher risk of later disability to inform current treatment decision making but also inclusion in future research studies.

Public: It is important to ensure that this proposal has an impact on the wider public locally and beyond. One outcome from this proposal would be better insights into collagen processing. Hence, principles learnt from such research can be applied more broadly to degenerative osteoporosis which has a large disease burden in an elderly population.

International audience: This proposal would benefit international centres with large OI patient cohorts (ERN Bone specialist centres, Shriners Hospital, Montreal; NIH, Bethesda, the Collagen Diagnostic Laboratory, Seattle).

Commercial exploitation. *(Where relevant to your GeCIP) Genomics England has a very explicit intellectual property policy. We and other funders need to know if the proposed research likely to generate commercially exploitable results. Do you have commercial partners in place?*

We do not have any commercial partners at present.

References. *Provide key references related to the research you set out.* (Individual referred to above are shown in **bold; ***corresponding author)

Balasubramanian M*, Cartwright A, Smith K, Arundel P, Bishop NJ. Copy number variants in association with type 1 collagenopathy: Atypical osteogenesis imperfecta. Am J Med Genet A. 2016 170A(2):476-81. doi: 10.1002/ajmg.a.37431. Epub 2015 Oct 15.

Balasubramanian M*, Sobey GJ, Wagner BE, Peres LC, Bowen J, Bexon J, Javaid MK, Arundel P, Bishop NJ. Osteogenesis imperfecta: Ultrastructural and histological findings on examination of skin revealing novel insights into genotype-phenotype correlation. Ultrastruct Pathol. 2016 Mar-Apr;40(2):71-6. doi: 10.3109/01913123.2016.1140253. Epub 2016

Balasubramanian M*, Pollitt RC, Chandler KE, Mughal MZ, Parker MJ, Dalton A, Arundel P, Offiah AC, Bishop NJ. CRTAP mutation in a patient with Cole-Carpenter syndrome. Am J Med Genet A. 2015 Mar;167A(3):587-91. doi: 10.1002/ajmg.a.36916. Epub 2015 Jan 21.

Undiagnosed Skeletal dysplasia

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	Undiagnosed Skeletal dysplasia

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

While over 50% of skeletal dysplasias have been resolved, a number of recognized diseases remain unresolved or have sub-groups of patients without recognized pathogenic mutations. Further, ultra-rare patients with constellations of skeletal and extra-skeletal features that do not map to existing classification systems also reach clinical attention.

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

Key to this subdomain:

1. *dREAMS as this provides a standard radiographic description of the patient and comparison to known 'genetically-defined' conditions in the existing database (see below)*
2. *Functional validation of bioinformatically/genetically prioritised variants will be undertaken using a pipeline of model systems with increasing complexity to ensure that only 'verified' variants progress to the next stage of analysis. The gold-standard of developing a transgenic mouse model will be applied only to those variants that have been functionally validated in simpler model systems.*
3. *iPS cell generation and re-programming to relevant cell types will provide an important model system for functional validation. Correction of the proven disease causing variant will be undertaken . These cell line will also be important pre-clinical models for drug testing/repurposing*
4. *Collaborate with MRC Harwell for mouse model generation, but can also be undertaken in-house.*
5. *Develop within the RUDYstudy a platform for syndromes without a name that captures both cross-sectionally and longitudinally significant clinical events and measures of health care usage.*

Collaborations including with other GeCIPs. *Outline your major planned academic, healthcare, patient and industrial collaborations. This should include collaborations and data sharing with other GeCIPs. Please attach letters of support.*

Paediatric, Ethics, validation,

At this early stage we have not arranged formal collaboration with any GeCIP, as we anticipate that there may be overlap with the paediatric GeCIP.

Training. *Describe the planned involvement of trainees in the research and any specific training that will form part of your plan.*

This could involve PhD students learning genomic editing and deep-phenotyping of a variety of model systems.

Beneficiaries. *How will the research benefit patients and healthcare institutions including the NHS, other researchers in the field? Are there other likely beneficiaries?*

Patients and their families benefit from having a genetic diagnosis that may explain the current clinical condition, prognosis and highlight potential complications in the future. It also provides a recurrence risk for the proband and their family.

Clinicians: This work package may lead to the identification of novel diseases that will inform clinical diagnosis both nationally and internationally as well as identification of individuals with existing diseases but not considered by the clinician due to atypical clinical presentations. In addition to patients, clinicians all over will benefit from earlier and more effective methods to diagnose and treat condition, thanks to the advancement of clinical and scientific knowledge.

Patient support groups: We will work with SWAN UK as appropriate.

Public: It is important to ensure that this proposal has an impact on the wider public locally and beyond. One outcome from this proposal would be better insights into diseases mechanisms that could be applied to more common diseases.

Commercial exploitation. *(Where relevant to your GeCIP) Genomics England has a very explicit intellectual property policy. We and other funders need to know if the proposed research likely to generate commercially exploitable results. Do you have commercial partners in place?*

We do not have any commercial partners at present

References. *Provide key references related to the research you set out.* (Individual referred to above are shown in **bold; ***corresponding author)

Javaid MK, Forestier-Zhang L, Watts L, Turner A, Ponte C, Teare H, et al. The RUDY study platform - a novel approach to patient driven research in rare musculoskeletal diseases. Orphanet J Rare Dis. 2016;11(1):150.

dynamic Radiological Electronic Atlas of Malformation Syndromes (dREAMS)

Full proposal (total max 1500 words per subdomain)	
Imaging Subdomain: Title *(max 150 characters)*	dynamic Radiological Electronic Atlas of Malformation Syndromes (dREAMS)

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

The International Nosology and Classification of Genetic Skeletal Dysplasias recognizes 42 groups, encompassing 436 conditions [1]. Despite these groupings, definitive diagnosis of the skeletal dysplasias is complicated by the rarity of individual conditions, the large phenotypic and genotypic heterogeneity (different disorders may look similar, subtypes of the same disorder may look different, conditions caused by the same gene may look different), and by a lack of standardization in the medical vocabulary used to describe the clinical and radiological phenotypes.

An accurate diagnosis leads to tailored genetic confirmation, appropriate family counselling, understanding of disease pathways and development of novel therapies. It also supports research through precise assessment of radiological response to therapy and genotype/phenotype correlations.
Identification and adequate description of the sometimes subtle radiological findings is crucial to the diagnostic process. However, there are several difficulties which include:

1. The rarity and variability of conditions
2. Correctly defining the radiological phenotype. The use of different terminology by different radiologists/observers for the same radiological feature(s), may delay diagnosis, cause misdiagnosis and/or confound research data
3. Limitations of existing scoring systems for documenting the severity of these conditions
4. A lack of longitudinal clinical phenotype data

dREAMS will be an advanced patient database that describes patients' findings in carefully controlled terms. In particular, in dREAMS the terms and their relations (*i.e.* an ontology) will be designed to precisely reflect the language of radiographic description. Moreover, dREAMS will be a *temporal database*, designed to meet the needs of longitudinal disease study.

dREAMS will be a secure web-based system, comprising an appropriately structured database to hold the patient and image data and the associated meta-data. The overall corpus of patient data, in particular annotated radiographic images, will form an *Atlas*, or reference set of images and diagnoses that can support statistical analysis and assist with differential diagnosis.
To meet the project's objectives, the dREAMS platform requires development. The existing ontology must be refined to capture full details of the radiographic features of the rare musculoskeletal diseases.

The success of such an approach to the characterization and understanding of disease is well demonstrated by the Face2Gene [2] and particularly the Human Phenotype Ontology projects [3]. However, neither of these were designed to, nor do they, capture the imaging phenotype of disorders. If this GeCIP is to meet its aims, then it is important that we develop a specific radiological ontology.

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

Objectives:

- To develop an on-line annotated image archive and ontology based on the nominated musculoskeletal diseases within GEL
    - Choanal atresia
    - Chondrodysplasia punctata
    - Craniosynostosis
    - Kyphoscoliotic Ehlers Danlos syndrome
    - Multiple epiphyseal dysplasia
    - Osteogenesis imperfecta
    - Thoracic dystrophies
    - Undiagnosed skeletal dysplasia
    - Stickler syndrome
- To link the dREAMS ontology with the Human Phenotype Ontology (HPO)
- To document genotype-(radiological) phenotype correlations
- To assess the reliability of the dREAMS statistical algorithm to prompt a correct diagnosis in genetically proven cases

Methodology: (see also Gantt chart)

Image Analysis/Development of Ontology

- "Learning" cases will be annotated first (target: variable, but understanding that these are rare, a minimum of 20 cases per condition)
    - These are so-called "learning cases" because they will allow the dREAMS knowledgebase to "learn" the key ontological variables of the genetically confirmed "typical" conditions listed above
- "Test" cases will be annotated subsequently (target: variable but minimum of 30% of "learning" cases per condition)
    - These are so-called "test cases" because they will allow us to determine the ability of the knowledgebase to prompt a correct diagnosis of the genetically confirmed "typical" conditions listed above
- The radiological ontology will be developed and refined through an iterative process led by ACO in collaboration with other radiologists within the musculoskeletal domain
- Existing methods for on-line image annotation and curation for dREAMS (funded by Newlife Foundation and Skeletal Dysplasia Group for Teaching and EU FP7 SYBIL project) developed in close collaboration with Certus Tech Ltd [4]
- Statistical analysis techniques and their presentation will be iteratively applied

NOTE: We will fully develop and test the ontology for one condition before moving on to the next, in order to maximise the use and impact of dREAMS for analysis of data from the 100,000 Genomes project.

References:

1. Bonafe L, Cormier-Daire V, Hall C et al Nosology and classification of genetic skeletal disorders: 2015 revision Am J Med Genet A 2015;167:2869-2892
2. FDNA Dysmorphology Face2Gene http://www.fdna.com/face2gene/
3. The Human Phenotype Ontology http://human-phenotype-ontology.github.io
4. Certus Tech Ltd http://www.certus-tech.com/cta/Home

Data requirements

Data scope. *Describe the groups of participants on whom you require data and the form in which you plan to analyse the data (e.g. phenotype data, filtered variant lists, VCF, BAM). Where participants fall outside the disorders within your GeCIP domain, please confirm whether you have agreement from the relevant GeCIP domain. (max 200 words)*

It is probable that we will need access to all of the data types which might be available to us. Clearly, phenotype data and filtered variant lists will be the starting point of our analyses, but access to VCF and BAM files might be desirable in some instances. It is possible that variants will be identified in participants of other GeCIPs but in genes which are of interest to us, rather than to these other GeCIP. If that situation arises, we will seek agreement from the other GeCIPs.

However, we remain somewhat unclear about the procedures by which we might identify such patients in the first instance.

Data analysis plans. *Describe the approaches you will use for analysis. (max 300 words)*

- Derive variant calls for "simple" sequence changes
- Identify possible structural variants (large deletions, insertions, rearrangements & copy-number changes
- Filter variants against control data sets
- Annotate variants according to their predicted effect (altered protein sequence/expression level, RNA splicing, gene regulation, *etc.*)

Key phenotype data. *Describe the key classes of phenotype data required for your proposed analyses to allow prioritisation and optimisation of collection of these. (max 200 words)*

1. Human phenotype ontology
2. dREAMS ontology
3. Bone Histopathology and bone laboratory results
4. Patient reported symptoms, co-morbidities, medication history, fracture history and outcome measures (EQ5D-5L, SF36, Paindetect) from the RUDY study (NIHR RD TRC MSK national cohort study)
5. Orthopaedic procedures from OPSC-4 classification

Alignment and calling requirements. *Please refer to the attached file (Bioinformatics for 100,000 genomes.pptx) for the existing Genomics England analysis pipeline and indicate whether your requirements differ providing explanation. (max 300 words)*

We do not anticipate that our requirements will differ. The standard alignment and calling proposals appear to meet our needs.

Tool requirements and import. *Describe any specific tools you require within the data centre with particular emphasis on those which are additional to those we will provide (see attached excel file List_of_Embassy_apps.xlsx of the planned standard tools). If these are new tools you must discuss these with us. (max 200 words)*

There do not appear to be any tools which are described explicitly as being capable of converting the variant data in VCF files into standard HGVS-compliant variant descriptions. xBrowse (line 16 of the Excel spreadsheet) might be capable of doing this but there is no mention of this in the online documentation. Annovar (line17) will possibly perform this task correctly, but past versions have not done so. Perhaps Jannovar (https://charite.github.io/software-jannovar.html) should be added to the Embassy apps as it specifically claims "…provides HGVS-compliant annotations for both for variants affecting coding sequences and splice junctions as well as UTR sequences and non-coding RNA transcripts."

One of us (Raymond Dalgleish, University of Leicester) has developed a utility (vcf2hgvs) which will generate HGVS-compliant variant descriptions from VCF files. It is currently in beta testing but could be made available for this project following discussion of the issues.

Data import. *Describe the data sets you would require within the analysis environment and may*

therefore need to be imported or accessible within the secure data environment. (max 200 words)

This is difficult to predict and will depend upon the actual quality of the processed data and on any findings that we make with respect to our nominated patients. We will require access to VCF files for each of our patients in the study and may wish to request data with respect to patients from other GeCIPs who harbour candidate disease-causing variants which are found in our patient cohort. We might require access to corresponding BAM files.

We will need access to all patient phenotype data including previous genetics testing and images.

Computing resource requirements. *Describe any analyses that would place high demand on computing resources and specific storage or processing implications. (max 200 words)*

We do not anticipate that we will require storage or processing resources which would be considered as being exceptional. We will need to process VCF files and may have to undertake additional analyses of BAM files. It is unlikely that we will need to re-analyse raw sequence reads.

Omics samples

Analysis of omics samples. *Summarise any analyses that you are planning using omics samples taken as part of the Project. (max 300 words)*

In the first instance, we will be focused on the genome sequence data to identify new candidate genes. Whether we will need access to Omics data will depend entirely on the genes identified in the initial analyses.

Data access and security

GeCIP domain name	**Musculoskeletal**
Project title *(max 150 characters)*	**Using Whole Genome sequencing to understand and develop diagnostics and treatments for rare musculoskeletal disorders**

Applicable Acceptable Uses. *Tick all those relevant to the request and ensure that the justification for selecting each acceptable use is supported in the 'Importance' section (page 3).*

☑ *Clinical care*
☑ *Clinical trials feasibility*
☑ *Deeper phenotyping*
☑ *Education and training of health and public health professionals*
☑ *Hypothesis driven research and development in health and social care - observational*
☑ *Hypothesis driven research and development in health and social care - interventional*

☑ *Interpretation and validation of the Genomics England Knowledge Base*
☑ *Non hypothesis driven R&D - health*
☑ *Non hypothesis driven R&D - non health*
☑ *Other health use - clinical audit*
☑ *Public health purposes*
☑ *Subject access request*
☑ *Tool evaluation and improvement*

Information Governance

☑ The lead and sub-leads of this domain will read and signed the Information Governance Declaration form provided by Genomics England and will submit by e-mail signed copies to Genomics England alongside this research plan.

Any individual who wishes to access data under your embassy will be required to read and sign this for also. Access will only be granted to said individuals when a signed form has been processed and any other vetting processes detailed by Genomics England are completed.

Other attachments

Attach other documents in support of your application here including:

Cover letter

Dr M Kassim Javaid

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1.12.2016

Dear GEL

Reg: MSK GeCIP research plan

Please find enclosed our research plan that combines existing international expertise within the UK in clinical phenotyping, radiology, functional studies using model organisms and health economics. We are working to develop a programmatic model of research from initial patient characterization both cross sectionally, longitudinally and radiographically to functional validation and economic evaluation of genomic technologies within this disease area.

The GeCIP will submit to Wellcome an application to support this work led by Prof Briggs through a series of workpackages, focusing on MED, bone fragility and undiagnosed dysplasias.

We are happy to supply further details as required.

Yours sincerely

Dr M Kassim Javaid

Associate Professor in Metabolic Bone Disease
University of Oxford