3D Photography of Cleft Lip: Applying Imaging Biomarkers Pre- and Post-operatively to Facilitate a Precision Medicine Approach

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1. Introduction: Prevention vs Treatment of Cleft Lip

Orofacial clefts are amongst the most common Craniofacial Anomaly (CFA) occurring with a birth frequency of approximately 1 in 700 live births and demonstrating significant ethnic and geographic variation[1]. They can be broadly categorised as syndromic (30%) or non-syndromic (70%) with the latter comprising a range of disorders anatomically confined to the lips and oral cavity and referred to as Cleft Lip (CL), Cleft Lip and Palate (CLP) and isolated Cleft Palate (CP)[2] *(Figure 1.).* Epidemiological studies into the aetiology of orofacial clefting suggest that CL +/- CP is an entity distinct from isolated CP with both resulting from a complex interplay of environmental and genetic causative factors influencing cardinal developmental events *in utero*[3]. Yet whilst the ultimate goal may be considered by some to understand cleft aetiology with a view to prevention[4], the existence of both single-gene and polygenetic inheritance factors - in combination with undefined environmental influences - renders this goal extremely challenging. Notwithstanding preventative efforts, there is considerable room to optimise the cleft treatment pathway and improve surgical outcomes, and this is an area in which the UK has lead globally through the publication of two key reports focussing on the structure and delivery of cleft services[5] [6]. We are now entering the next phase of improvement which, in concert with the rest of medicine, involves a precision-medicine approach to cleft lip. This, in turn, demands comprehensive characterisation of both baseline and post-operative cleft conditions - and it is in this regard that 3D photography is a critical adjunct.

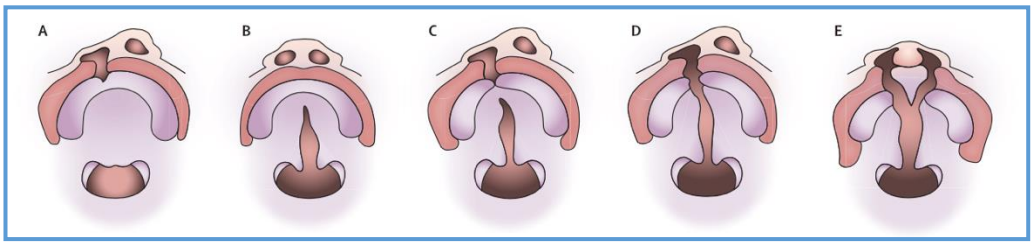

Figure 1. Non-syndromic orofacial clefts[3]

(A) Cleft lip and alveolus

(B) Cleft palate

(C) Incomplete unilateral cleft lip and palate

(D) Complete unilateral cleft lip and palate

(E) Complete bilateral cleft lip and palate

2. The Challenges of Classification & Measuring Treatment Outcome

Treatment of CLP is multidisciplinary in nature and spans from birth until adulthood. It addresses the effects of the disorder on appearance, speech, hearing and cognition that would otherwise impact severely on the psychosocial integration of those affected[7]. A significant component of cleft care is surgical in nature and can be broadly categorised as ‘primary’ or ‘secondary’ despite a multitude of surgical protocols[8]. In general, primary surgery usually occurs within the first year of birth and is corrective of the CL or CP defect. Secondary surgery is undertaken with increasing maturity to revise or augment earlier procedures or to address more complex growth disturbances of the face[9]. The lack of evidence to assess the outcomes of either primary or secondary surgery underpins the contentious variation in surgical practice that is observed not only worldwide but nationally.

Though often considered a problem distinct from that of cleft classification, measurements of cleft surgery outcome are inextricably linked to how clefts are classified for it is the baseline (pre-operative) phenotype upon which a surgical protocol is predicated and against which surgery-induced changes should be measured. Classification of non-syndromic orofacial clefts has remained a challenge reliant on broad verbal phenotypic descriptors. Several excellent publications have reviewed the evolution and interplay of various classification systems[10 11]. The more

recent of these call for a revised classification of CL/P to fully recognise the heterogeneity of phenotypes and sub phenotypes so crucial to advancing research in an era of customised treatment[12]. Indeed, the challenges of baseline phenotypic classification and appraisal of surgical outcomes can be unified by our limited ability to describe the cleft defect for detailed analysis, whether before or after surgical intervention. The use of 3D photographic technology, however, and advances in morphometric analysis have the potential to revolutionise our approach to pre-operative cleft classification, post-operative outcomes analysis and, indirectly, our approach to genetic characterisation.

3. 3D Photography and Cleft Lip

When 3D photographic technology was initially launched in the cleft realm it was likely underestimated by some as just a modernisation of regular 2D photography and an improved method to record the cleft defect at various stages throughout treatment[13] [1]. Yet in an era of machine learning and ever-increasing speeds of high-yield data analysis, it is potentially far more impactful than 2D photography could ever be[14].

3D photography has many advantages: it is non-invasive and radiation-free and can capture a 3D image in milliseconds, properties that make it ideally suited for recording the cleft defect in babies and growing children. The resulting image can be manipulated to facilitate innumerable views with ease - but more than that it can be *analysed* in a way that 2D photographs cannot be. Each 3D photo contains a surface texture map overlying a 3D polygonal mesh, defined by a multitude of nodes, each themselves characterised by a set of 3D co-ordinates in space *(Figure 2)*.

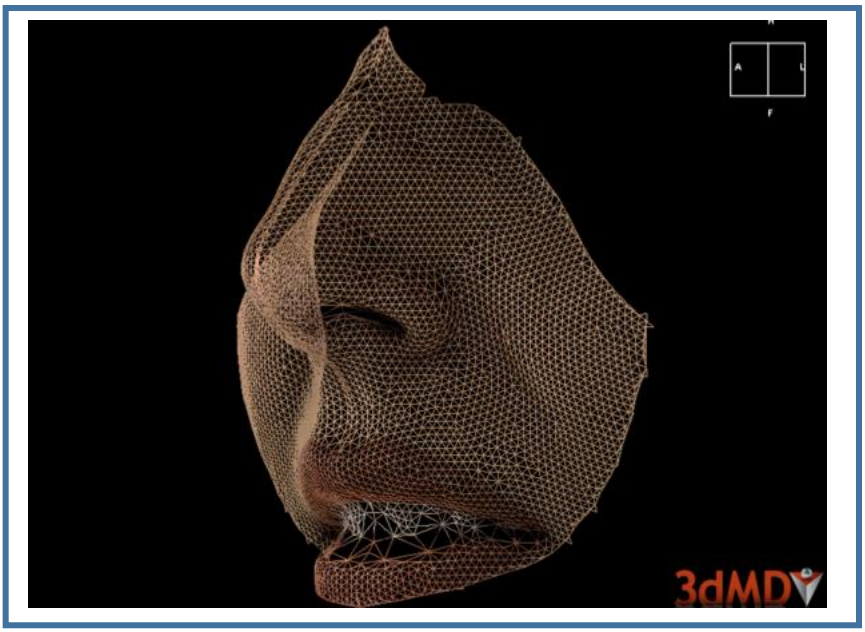

Figure 2. Mesh view of a cropped 3D photographic image of a child with unilateral CL

A photo therefore contains a huge amount of data that can be analysed through various mathematical means, likely automated, with potential for summation and index generation. With ever-evolving hardware and software, 3D photography is rapidly gaining popularity as a means for recording the cleft defect despite the significant investment required for its implementation. Indeed, a systematised scoping review of the last decade's research literature of all methods used to record the cleft defect has demonstrated that 3D photography has surpassed the critical "tipping point" in its technology diffusion curve[15]. A second systematic review has demonstrated that the effect of 3D photography within cleft presently exists at the level of influencing clinical thinking and decision-making [16] (Level 3 in Fryback and Thornbury's diagnostic hierarchy[17]) though it is likely that once the full potential of 3D photography is realised this level of influence will increase to directly impact on surgical protocol to optimise surgical outcome.

So, what exactly is this potential aside from recording 3D pictures?

4. Using 3D Photography to Assess Post-Operative Cleft Lip Outcomes

3D Photographs of post-operative cleft lip patients can be mathematically analysed to provide an objective means for measuring post-operative outcomes in cleft surgery.

In cleft lip, facial appearance is one domain for which surgery is the main component of treatment [18]. This has given rise to many outstanding questions to be answered such as: whether the severity of a cleft lip defect at pre-operative baseline influences the outcome of primary (corrective) surgery[19] [20], to what extent secondary growth disturbances affect facial appearance[21] and what is the influence of surgical protocol and surgical skill on appearance-related outcome[22] ? Measuring facial outcomes, however, is challenged by the immense social significance of facial appearance and its subjective interpretation in terms of facial attractiveness. This has given rise to a number of evaluative approaches which can be considered to lie on a subjective-objective continuum. At the subjective extreme is the emphasis on the patient's perspective of 'health outcomes'[23] via Patient Reported Outcomes Measures (PROMS), with adaptation to facial appearance in cleft having been recently validated[24][25].

Whilst a patient-centred approach has many benefits this may not be appropriate for evaluating all aspects of cleft treatment; many surgeons question how PROMs can facilitate a *timely* improvement in their surgical protocols. Such concerns likely relate to aspects unique to surgery as a treatment and it's timing in relation to evaluation. As surgical correction of CL occurs in the neonatal period, with subsequent surgery occurring throughout childhood and beyond, patients are yet to experience many of the critical psychosocial events that shape the 'self-concept' so central to patient-centred assessments of facial appearance[26]. And whilst there is an emerging body of paediatric-specific PROMS[27] [28], application is contingent on a minimum level of patient co-operation and communication - both not fully developed in the young child undergoing CL surgery. Several of the health outcomes relating to facial appearance, therefore, only manifest for assessment some considerable delay after surgical intervention. Furthermore, it is difficult to isolate the influence of a given surgical variable within the context of a 'health' outcome designed to reflect facial

appearance, given all other confounding variables. Thus whilst health outcomes are valuable in appraising some aspects of cleft care, in order to advance cleft lip surgical protocols, it is a 'treatment' outcome that is required[29]. This may be best served by an objective approach.

5. The Objective Approach to Cleft Facial Appearance Assessment: Development of Image-based Biomarkers

Objective approaches rely on the analysis of a record of the cleft defect which can be summarised in an index. 3D photography has revolutionised this approach and a recent review underway by our group has demonstrated that the main methods of 3D photographic facial analysis in cleft patients are those based on facial symmetry, facial averageness, facial volume and facial shape[30]. These methods are becoming ever more refined and sophisticated as a result of advances in both 3D photographic hardware, such as portable cameras, and software. Indeed, 3D photographic facial assessment is now less limited by data capture and analysis speeds but rather by the lack of clinimetric rigour applied during the process of developing summative indices[31]. Whilst much clinimetric theory has been developed in the context of subjective measures of outcome, such as the COSMIN checklist[32], many components are transferable and applicable to the development of objective outcome measures too.

In addition to a clinimetric approach there needs to be a recognition that facial appearance indices are none other than Image-based Biomarkers and, as such, they should be subjected to formal statistical assessments of validation akin to the development of biomarkers and surrogate markers[33] in other areas of medicine[34 35 36]. Only once meaningful correlation between objective facial analysis and subjective endpoints have been demonstrated can the full diagnostic utility of 3D photography in cleft be realised, so advancing its potential to impact treatment protocols[37]. Thus far from being considered mutually exclusive, subjective and objective approaches to post-operative CL facial evaluation should be viewed as integrated and complementary *(Figure 3.)*

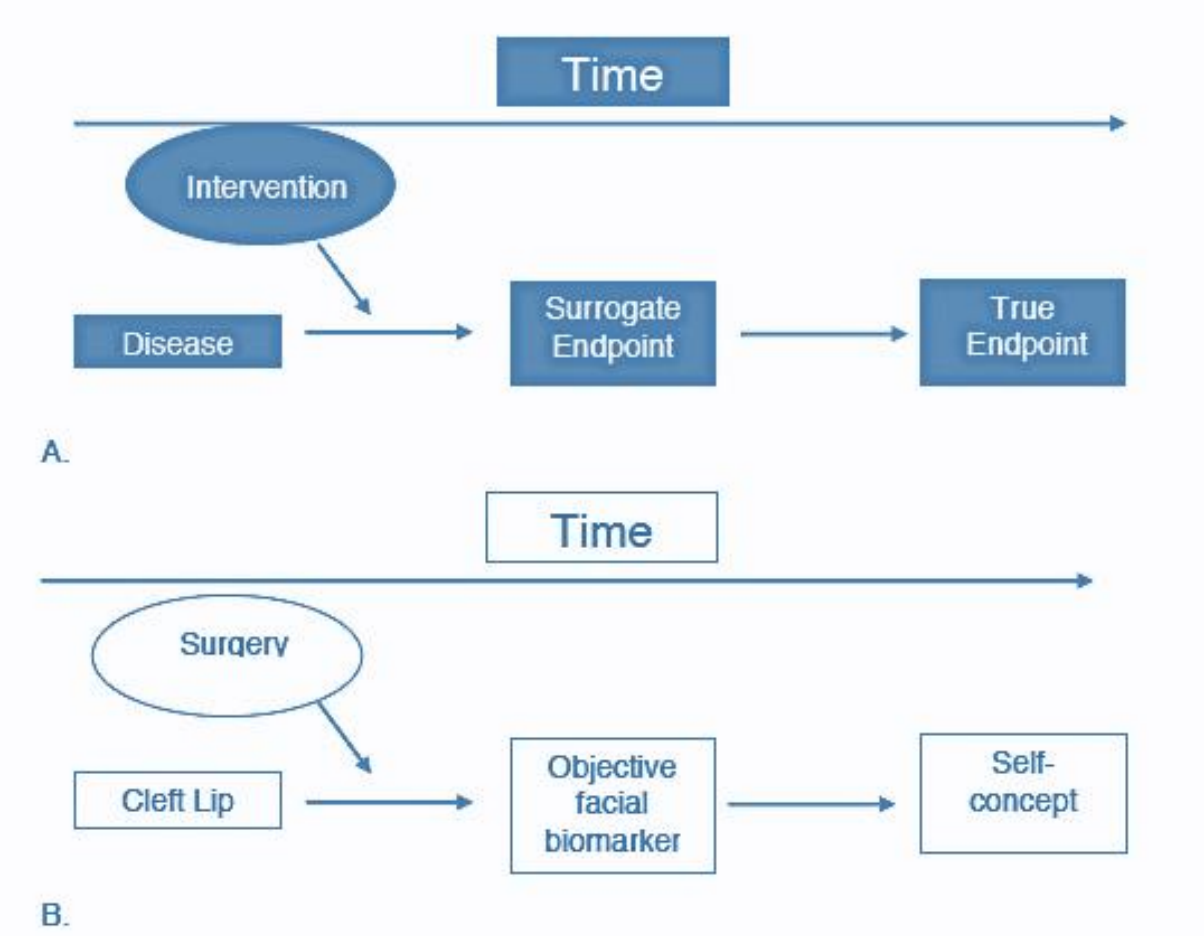

Figure 3: Relationship between disease, treatment, Surrogate End Point (SEP) and True Endpoint (TEP) in A. general B. as applied to Cleft Lip (CL)

6. Using 3D Photography to Deep Phenotype the Cleft Lip Defect

A hitherto undemonstrated application of 3D photographic analysis is to classify un-operated cleft lip faces using a mathematically-derived ontology.

Cleft Lip (CL) demonstrates a wide phenotypic spectrum currently described by a limited set of verbal categories *(Figure 4.)*. Whilst there are several classifications of the CL deformity[10], none is able to discriminate the three-dimensional shape of the deformity with adequate sensitivity to represent the full range of CL phenotypes observed[12]. This limits our ability to scale CL severity at pre-operative baseline and to comparatively assess post-operative outcomes. Furthermore, it prevents the

meaningful stratification of phenotypes necessary to accurately predict the natural progression of CL and the effects of treatment.

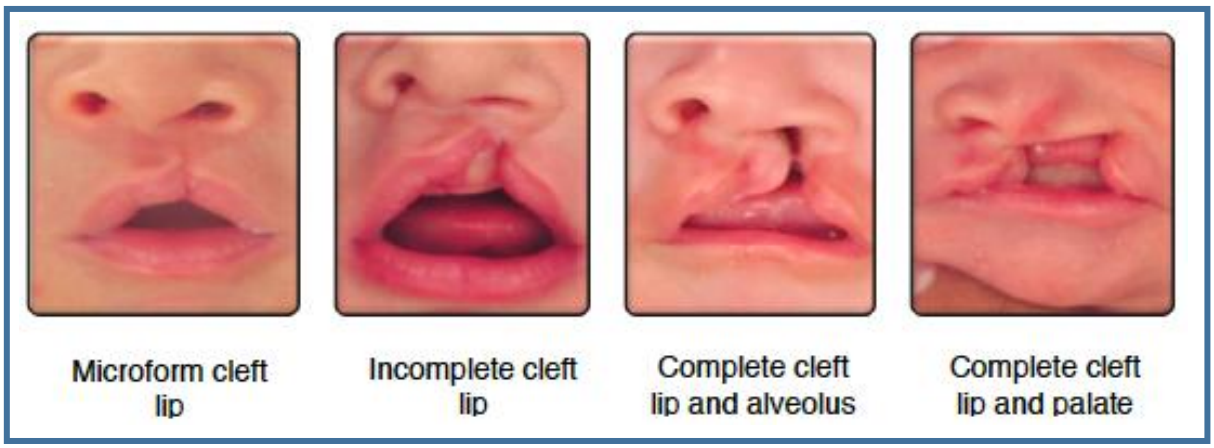

Figure 4: Examples of the CL phenotypic spectrum
Image taken from http://www.drderderian.com/unilateralcleftlipandpalate/

The comprehensive analysis of phenotype based on a higher resolution of phenotypic components is known as ‘deep’ or ‘extended’ phenotyping and is considered an essential counterpart to advancing genetic techniques in an era of a ‘precision medicine’[38]. Perhaps the most profound consequence of current CL phenotypic classifications, therefore, are the limitations imposed on the systematic study of CL phenotype / genotype correlations and hence the ability to customise CL care.

3D photographs of un-operated cleft lip can be used to deep phenotype the defect by using a combination of image analysis techniques (such as Dense Surface Modelling) and statistics (such as Cluster Analysis) to identify photographs that share similarities (clusters) from those that are markedly different (extremes) *[work in progress, Haers / Edwards group].* Such mathematically-defined similarities can then be compared to those perceived by the human eye. This initial multidisciplinary approach has been applied to the facial gestalt of other medical conditions with facial stigmata but not, to our knowledge[39] [40] [41], to the “cleft classification dilemma”[42]

(Figure 5). Our research group is currently deep phenotyping one of the largest cohorts of 3D cleft lip photographs using this combination of methods and further characterising identified groups by a probability distribution of principal facial features. By inputting new 3D photographs of cleft lip faces into the resulting algorithm and analysing the 'goodness of fit' with identified groups, the probability distributions defining each sub- and extreme- mathematical phenotype can be continually refined. This is an example of 'adaptive' learning - a variation of machine learning – and it is the future of cleft phenotyping.

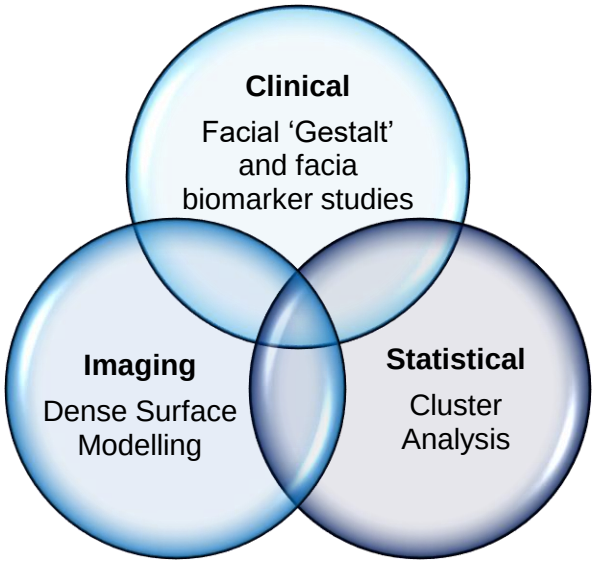

Figure 5: Multidisciplinary approach to classify CL

7. Impacts & Future Projections

Cleft Lip is the term used to describe a facial defect that has a variety of genetic causes and presentations. It has a variable natural progression and likewise responds to treatment protocols in a variety of ways. For the time being, this group of facial defects are coarsely labelled and treated surgically according to a protocol that is based more on surgeon preference than on evidence base. Clearly there is scope to refine the diagnosis and customise the treatment of cleft lip to the individual patient - in short to apply a precision-medicine approach to the condition.

I share in a future of cleft lip surgery in which a child born with cleft lip can immediately undergo minimally-invasive 3D photography at the bedside using a portable 3D photography machine. The resulting portfolio of photographs can then be analysed automatically using pattern recognition software that will compare the patient's photographic findings against those of a highly refined algorithm identifying validated sub-phenotypes and extreme phenotypes. Such phenotypes will have been characterised comprehensively for genetic origin, associated conditions (endophenotypes[41]), natural progression and evidence-based response to treatment. The result will be a detailed, precise diagnosis of that baby's cleft lip with recommendations for additional screening, genetic or otherwise, and a suggestion of optimal treatment algorithm. Those patients with particularly challenging prognoses can then be directed to centres super-specialising in their condition. When patients undergo surgery, the post-operative results will be serially recorded using 3D photography once more and analysed for outcome, generating information that can be used in conjunction with subjectively assessed outcomes.

Portable 3D photographic equipment already exists. Software for detailed facial analysis already exists and is becoming increasingly automated and powerful. And though surgery as a whole has been slow on the need to define and validate biomarkers research is underway to refine post-operative image-based biomarkers and validate them against subjective end-points. Deep phenotyping of the cleft defect has commenced in earnest, treading the path of other facial conditions that have been likewise characterised. It will not be more than ten years before we have an objective and validated method of describing both the un-operated and operated cleft lip face, facilitating deep phenotyping and post-operative outcomes assessment, respectively. This, in turn, will inform research into the natural history and treatment response of cleft lip patients through meaningful groupings of patients. It can also potentially facilitate a retrograde approach to genetic enquiries through the identification of sub- and extreme phenotypes of cleft lip to analyse genetically, as has been successfully pursued in other facial conditions[41 40 39].

Yet 3D photographic assessment of cleft lip is only the start of deep phenotyping and post-operative outcomes analysis. There are many other aspects to the characterisation of cleft lip appearance including aesthetic vs. functional aspects,

extra-oral vs. intra-oral components and static vs. dynamic assessments - all with the potential for genetic association. 3D photographs so described only assess the combination of aesthetic, static and extra-oral domains. With newer, real-time 3D photography (viodegraphy) technology and bracketing capabilities, however, it is now possible to characterise the cleft defect in dynamic extra-oral terms. As, and when, technology is developed to assess the remaining domains of cleft lip appearance, integration of all the derived information will result in the most comprehensive analysis of un-operated and operated cleft lip ever known.

8. Requirements

So what does it take for this vision of customised cleft lip diagnosis and treatment to become a reality and what are the challenges?

3D photographic equipment is already installed in many cleft units worldwide but our reviews has demonstrated that there is a significant variation in its distribution despite global diffusion beyond the technology “tipping point”. Certainly within the UK 3D equipment is installed in only a proportion of cleft departments and we are currently undertaking a survey to identify the determinants influencing this partial uptake. Cost implications are likely to feature as a significant reason but surprising there are several units where 3D photographs are not being routinely taken despite a facility present. Training of personnel, the lack of a 3D cleft photography protocol and the absence of consensus as to the utility of 3D photography in cleft treatment have all been identified as barriers to adoption[43]. To this end, our research group has collaborated with medical photographers based at the Institute of Medical Illustrators (IMI) to draft a protocol for 3D cleft photography that will be further refined through a Delphi Consensus study involving a multidisciplinary group comprising representatives of all disciplines allied to 3D photography and cleft. Ultimately, any case for routine 3D photography within all UK cleft units ought to demonstrate a cost-benefit feasibility though it is likely that the current use of 3D photography is a case of “Buxton’s Law” whereby the usual justification for implementation of a new

healthcare technology has already been usurped through partial adoption beyond a critical point[44].

Before 3D cleft photographs can be nationally generated and analysed, not least to further research into deep phenotyping and post-operative outcomes, there needs to be appropriate security measures and capacity for their storage. This is not a new problem to the UK's National Health System (NHS) but nonetheless demands funding and requisite IT infrastructure. Smaller scale projects, such as those associated with our research, show that regionalised hubs of data collection may suffice in the first instance. These should ensure sufficient numbers of 3D photographs to power studies into the validation of biomarkers, both with respect to subjective assessment as well as longer-term PROMs-derived assessments.

9. Summary

The development of 3D photographic-based facial appearance indices in cleft forces two paradigms shifts. The first of these is the consideration that such indices are effectively image-based biomarkers and, as such, should be subjected to the same clinimetric rigour and statistical testing as any other biomarkers in medicine if their full potential is to be realised[45]. This entails a validated correlation with subjective aspects of facial appearance in order to enable their use as a post-operative outcome assessment tool that can direct research and ultimately choice of treatment protocol. Secondly, biomarker assessments derived from 3D photographs of un-operated cleft faces can be distributed and characterised mathematically to 'deep' phenotype the defect[38]. Such information can identify groups based on mathematical assessment of appearance that can also be validated against subjective assessments. The groups can also be used to facilitate research into the natural history and treatment response by group. Most significantly, however, identified sub-phenotypes and extreme phenotypes can be used to direct research into genetic causation thus truly embracing the notion of precision medicine in cleft.

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