Progress and Research Priorities in Imaging Genomics for Heart and Lung Disease: Summary of an NHLBI Workshop

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ABSTRACT

Imaging genomics is a rapidly evolving field that combines state-of-the-art bioimaging with genomic information to resolve phenotypic heterogeneity associated with genomic variation, improve risk prediction, discover prevention approaches, and enable precision diagnosis and treatment. Contemporary bioimaging methods provide exceptional resolution generating discrete and quantitative high-dimensional phenotypes for genomics investigation. Despite substantial progress in combining high-dimensional bioimaging and genomic data, methods for imaging genomics are evolving. Recognizing the potential impact of imaging genomics on the study of heart and lung disease, the National Heart, Lung, and Blood Institute convened a workshop to review cutting-edge approaches and methodologies in imaging genomics studies, and to establish research priorities for future investigation. This report summarizes the presentations and discussions at the workshop. In particular, we highlight the need for increased availability of imaging genomics data in diverse populations, dedicated focus on less common conditions, and centralization of efforts around specific disease areas.

Keywords: Genomics, imaging, prevention, cardiovascular disease, metabolites, proteins

A. INTRODUCTION

The burden of heart and lung disease remains immense despite the substantial progress made by large scale population-based initiatives such as primary prevention statin therapy[1] and smoking cessation[2]. Advancing the prevention of heart and lung diseases depends on identifying individuals at increased risk and targeting lifestyle modifications or medical therapies to reduce the progression or consequences of the condition. Multivariable risk prediction models provide accurate assessments at the population level, but individual-level risk prediction remains challenging;[3] many events occur in individuals determined to be at low risk[4]. Methods that more precisely identify heart and lung disease risk and its biological determinants are needed to reduce these disorders.

Genomics assesses how variation in the genetic code contributes to phenotypic heterogeneity. In heart and lung diseases, genetic mutations have been identified to contribute to numerous (usually rare) conditions, and ever-larger genome-wide association (GWA) studies seek to associate genetic variation (common and rare) with common clinical phenotypes. Actionable insights from genetic association studies depend on mapping genetic risk variants to specific clinical phenotypes or discrete pathophysiologic mechanisms to identify true causal variants. However, the identification of true causal genetic variants is challenging with traditional GWA studies when there is high correlation among variants in close proximity to each other (linkage disequilibrium) or because a large number of variants identified by GWA studies map to intergenic areas[5]. Moreover, common heart and lung diseases are heterogeneous conditions rendering GWA studies inherently less powerful both statistically and with regard to gaining potential mechanistic insights. Precise clinical phenotyping is crucial to disentangle genetic drivers of heart and lung diseases.

Progress in bioimaging, assisted by computational advances and the use of artificial intelligence (AI) technologies, enables identification of more precise imaging features to serve as intermediate and/or advanced phenotypes for genetic analyses. The synergy between bioimaging and genomics lies in the fact that modern molecular and statistical genetics methods embrace quantitative phenotyping (i.e., description of traits on a continuous scale). Contemporary bioimaging methods provide phenotypic measurements with exceptional resolution (e.g., three-dimensional spatial sampling of 100-500 microns), and, therefore, are ideally suited as quantitative high-dimensional phenotypes. By combining state-of-the-art bioimaging techniques with genomic information, the emerging field of *imaging genomics* seeks to elucidate the genomic architecture of bioimaging traits. With higher resolution of both genomic interrogation and bioimaging phenotypes, imaging genomics has the potential to

resolve heterogeneity in the phenotypic expression associated with genomic variation, improve disease risk prediction, discover novel prevention approaches, and enable precision diagnosis and treatment (**Figure 1**).

The National Heart, Lung, and Blood Institute convened a workshop in October 2019 in recognition of this rapidly evolving field with the aim of bringing together a multi-disciplinary group of experts to review the latest cutting-edge approaches and methodologies in imaging genomics studies in heart and lung diseases, and to establish research priorities for the next phase of imaging genomics investigations[7]. In the following report, we summarize the presentations and recommendations from the workshop to provide a resource to serve as a roadmap of for the next phase of imaging genomics investigations.

B. IMAGING MODALITIES AND PHENOTYPES IN HEART AND LUNG DISEASES

Imaging genomics analyses rely on robust, reproducible, and clinically relevant discrete and quantitative imaging traits. The more precisely these imaging traits reflect underlying molecular mechanisms explained by genomic variation, the higher the expected yield of imaging genomics findings may be. A detailed review of imaging techniques themselves is beyond the scope of this workshop report. In this section, we review common imaging modalities used in heart and lung diseases with a focus on imaging techniques that are being used, or may be used in future studies, as quantitative traits for imaging genomics analysis (**Table 1**).

Imaging of the heart and vasculature

Computed tomography (CT)

CT imaging can be performed rapidly with minimal radiation exposure and provides detailed assessment of cardiovascular structures with high spatial resolution[8]. Calcium burden in the coronary arteries (coronary artery calcium, CAC), great vessels, or cardiac valves can be detected by CT imaging without intravenous contrast (or by other imaging techniques such as chest X-ray[9]) and each of these traits is associated with risk of future cardiovascular events[10,11]. Accordingly, imaging investigations have evaluated the genomic determinants of vascular and valvular calcification. Initial GWA studies for CAC identified single nucleotide variants (SNVs) that were also associated with clinically apparent coronary artery disease[12,13], lending support to the clinical (and pathogenetic) overlap of CAC and clinical atherosclerotic events. Translation of these findings to clinical risk prediction or identification of novel therapeutic targets has been limited by lack of linkage to disease-causing mechanisms[5]. Calcification of other arterial sites is also associated with cardiovascular risk. Recently, investigators identified SNVs within the

HDAC9 gene to associate with aortic calcification[14]. HDAC9 knockout mice displayed reduced aortic calcification indicating that HDAC9 may be an important regulator of vascular calcification. In addition, calcification in the aortic valve is easily obtained from CT, reproducible, and represents an earlier stage in aortic valve disease that predicts future clinical aortic stenosis[11]. GWA studies of aortic valve calcium linked SNVs in the apolipoprotein(a) gene to aortic valve calcification[11] and to clinical manifestations of aortic stenosis[15]. Clinical trials are now testing the hypothesis that pharmacologic lowering of circulating apolipoprotein(a) levels leads to reductions in aortic stenosis[16]. As shared risk factors and disease co-occurrence challenge the separation of causal factors for atherosclerotic CVD and calcific aortic stenosis in observational studies, this interventional trial may be particularly informative.

CT imaging of the coronary arteries with intravenous contrast (CT angiography) can provide detailed assessment of coronary plaque burden, location, and morphology, and the degree of blood flow obstruction as well as integrative measures such as fractional flow reserve and plaque characterization[8,17,18]. Whereas the requirement for intravenous contrast and technical expertise required for image acquisition has limited the availability of coronary CT angiography in large community-based cohorts, smaller studies have associated coronary stenoses by CT angiography with family history of coronary heart disease[19,20]. Future studies of larger samples will be important to elucidate genetic markers of relevant atherosclerotic plaque characteristics.

Echocardiography

Echocardiography provides detailed assessment of cardiac structure and function without exposure to contrast agents or radiation. As the clinical syndrome of heart failure progresses through stages of asymptomatic structural and functional cardiac remodeling, echocardiographic traits are important for imaging genomic studies of heart failure. Toward this end, GWA studies of echocardiographic traits have identified numerous SNVs, genes, and pathways linked with cardiac structural remodeling and heart failure risk[21-25].

Imaging genomics has been used to discover rare variants associated with cardiomyopathy phenotypes, such as dilated cardiomyopathy (DCM). DCM is defined as enlarged left ventricular dimensions with reduced left ventricular function. The most common underlying genetic cause of DCM is truncation variants in the *TTN* gene, which encodes the sarcomeric protein titin[26]. There is not one common variant underlying DCM but rather there are many individual *TTN* truncations that are each rare in the population. In aggregate, 1-2% of the general population carries *TTN* truncations, which are associated with subclinical

echocardiographic features, such as lower ejection fraction, and demonstrate ten-fold enrichment in DCM cases[27,28]. Importantly, not all *TTN* truncation carriers manifest with a cardiomyopathy phenotype. Taking a genotype-first approach, one study queried the electronic health record for diagnoses associated with *TTN* truncations and uncovered a higher prevalence of heart failure, atrial fibrillation, and paroxysmal non-sustained ventricular tachycardia in the absence of manifest DCM[29]. This 'genotype-first' view provides an estimate of the phenotypic expressivity of genetic variants and offers a broader assessment of the range of clinical diagnoses linked to a given genetic signature. In addition to *TTN* truncation variants, mutations in at least 50 genes lead to inherited cardiomyopathies, and each is associated with variable expressivity[30].

Future genomic studies of echocardiographic traits may use additional echocardiographic measures, such as strain imaging[31] or cardiac microstructure[32], as well as enhanced clinical phenotyping.

Cardiac magnetic resonance imaging (CMR)

CMR provides detailed structural and functional assessment of the heart and great vessels and can be performed efficiently in large community-based studies[33]. Indeed, CMR is being performed in the UK Biobank with a planned enrollment of 100,000 individuals[34]. In a report of the first ≈36,000 participants with CMR data, GWA identified 57 different genetic loci that were associated with cardiac structure and function[35]. A polygenic risk score derived from these loci was associated with dilated cardiomyopathy risk. Besides measuring heart structure and function, dedicated CMR imaging protocols can be used to evaluate specific cardiac features such as inducible myocardial ischemia[36], inflammation and fibrosis[37], and findings suggestive of specific underlying disease states[38,39]. The capability of CMR to accurately measure cardiac structure and function and complementary detailed imaging phenotypes makes it important for future imaging genomics studies.

Molecular imaging of the heart

Molecular imaging leverages targeted tracers labeled with an imaging reporter to identify specific biological processes[40]. For the assessment of coronary plaque activity, tracers can be used to assess vascular inflammation (18F-fluorodeoxyglucose with PET imaging[40,41] or ultra-small superparamagnetic particles of iron oxide imaged with CMR[42]), or microvascular calcification (representing active inflammation and higher risk for plaque rupture and identified by the 18F-fluoride PET tracer[43]). PET imaging can also be used to assess myocardial

perfusion, metabolism[44], and energetics[45]. Other imaging techniques such as magnetic resonance spectroscopy or imaging the cardiac sympathetic nervous system[46], may provide insight into disease activity and status. These emerging imaging techniques allow linkage of genetic variation with discrete biochemical processes. However, the feasibility of conducting these studies at the scale necessary to facilitate genetic interrogation is yet unproven.

Lung imaging phenotypes

Chest CT

Chest CT imaging provides excellent spatial resolution of lung architecture and diagnosis of chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), emphysema, and interstitial lung disease (ILD). Qualitative chest CT assessments used in clinical practice are being expanded to allow phenotypic characterization of early disease states. Additionally, quantitative chest CT imaging approaches facilitate association with environmental exposures and genomic variation in large consortia, such as COPDGene[47], SPIROMICS[48], and the MESA Lung Study[49].

Initial imaging genomic assessments of COPD and emphysema used volumetric chest CT scans to generate measures of emphysema as defined by the percent of lung occupied by low attenuation areas (LAAs; regions with less than -910 or -950 Hounsfield Units [HU])[50]. Other quantitative chest CT measures can be used for imaging genomic analyses, including airway wall thickness and luminal diameter, small vessel pruning, large artery characteristics, gas trapping, bronchiectasis, and fibrosis, among others[47]. Subsequently, GWA studies have assessed quantitative measures of emphysema overall[51,52] (including its patterns[53,54] and distribution[55]) in conjunction with other airway phenotypic assessments[48,56,57]. While GWA studies of quantitative chest CT measures have made important discoveries, the largest COPD GWA studies have focused on spirometry, which is more readily available in large numbers of individuals. In the largest COPD GWA study to date (comprising more than 335,000 participants) 82 independent loci were associated with COPD defined by spirometry[58]. Some of these loci are more strongly associated with measures of emphysema (e.g., *FAM13A* and *HHIP*), or airways measures (e.g. *HTR4* and *RASEF*) separately, while others (e.g., *EEFSEC* and *MFAP2*) are associated broadly across phenotypes[58]. Increased sample sizes and wider availability of quantitative CT phenotypes will improve our understanding of the genetic architecture of COPD.

Qualitative and quantitative chest CT imaging assessments can also identify features associated with early forms of interstitial lung disease (ILD). Interstitial lung abnormalities (ILA;

recently formally defined by the Fleischner Society[59]) are qualitative chest CT assessments suggestive of underlying ILD or pulmonary fibrosis in individuals not previously suspected of having ILD. Efforts to identify ILD In its early stages may improve detection and prevention methods for diseases such as idiopathic pulmonary fibrosis (IPF), the most common and severe form of ILD with a mortality rate rivaling many malignancies[60]. ILAs therefore represent valuable phenotypes for imaging genomics analyses. Variants in the promoter region of the mucin 5B gene (*MUC5B*; a common variant that may explain as much as 30% of IPF risk[61]) have been consistently associated with ILAs[62-64]. A recent GWA study demonstrated four additional loci associated with both ILA and IPF (including those near genes *DDP9*, *DSP*, *FAM13A*, and *IVD*)[64]. This study also demonstrated novel genetic loci associated with ILAs but not with IPF suggesting that visually detected ILAs likely includes phenotypically heterogeneous subsets, some of which may not correlate with overt IPF[64].

Quantitative efforts to identify early stages of ILD and pulmonary fibrosis include assessments of high attenuation areas (HAAs; typically between -600 and -250 HUs), local histograms (referred to as “interstitial features”), and deep learning-based lung textural assessments of lung fibrosis[65,66]. These quantitative chest CT features can potentially detect, characterize, and grade early stages of pulmonary fibrosis. However, these measures are not interchangeable, demonstrate varying degrees of sensitivity and specificity when compared to visual assessment of pulmonary fibrosis[66,67], and can be affected by technical differences between studies.

Molecular imaging of pulmonary fibrosis

Molecular probes targeting several components of pro-fibrotic pathways are under development for imaging fibrotic activity in IPF. By discovering early activity in pulmonary fibrosis before it is apparent by CT imaging, these molecular probes may identify earlier forms of the disease prior to overt lung fibrosis and can potentially be used to assess therapeutic responses to antifibrotic agents.

Molecular probes have been developed for type I collagen, a primary component of fibrosis (^{68}Ga-CBP8)[68] and for collagen cross-linking (Gd-CHyd)[69]. In clinical studies, patients with IPF had increased lung uptake of ^{68}Ga-CBP8, but it was also found in areas of normal appearing lung suggesting that ^{68}Ga-CBP8 may be sensitive in detecting regions of active collagen deposition prior to manifest fibrosis evident on CT imaging[70]. Probes also target drivers of fibrosis, such as integrin $\alpha_v\beta_6$[71], and the C-X-C chemokine-receptor type 4 (CXCR4)[72]. Somatostatin receptor 2 is expressed on fibroblasts and increases in fibrosis[73]. Somatostatin

receptor expression in humans with pulmonary fibrosis can be assessed using ^{111}In-octreotide scintigraphy (Octreoscan) and ^{68}Ga-DOTANOC PET-CT[74,75]. Beyond fibrosis-specific pathways, broader processes such as vascular leak[76], coagulation, and inflammation have been implicated in the development of pulmonary fibrosis and each can be assessed with specific molecular probes[77-80]. Similar to molecular imaging of the heart and vasculature, molecular imaging of the lungs is not yet being done at the scale necessary for GWA studies.

C. ARTIFICIAL INTELLIGENCE FOR BIOIMAGING

Terminology and methods

AI is a general term describing disciplines that aim to mimic human intelligence[81]. Here, we focus on the relatively narrow functions of data interpretation and risk prediction, but AI technologies capable of accomplishing complex human tasks are also being developed and may have additional wide-ranging applications[82]. At the core of AI is machine learning (ML), which uses mathematical models to substitute for human thought and decision-making. ML algorithms take inputs (e.g., clinical characteristics) and map them to given outputs (e.g., mortality), optimizing the fit of the model to achieve optimal performance. ML models are not explicitly programmed to achieve a given task. Instead, they minimize the *'cost'* of the model (the proportion of misclassified patients)[81]. This is regarded as the *learning* process of ML algorithms. Accordingly, ML algorithms gradually increase their accuracy as they 'see' and 'learn' from more data.

Application of AI for identification of anatomical structures and pathologies

Deep learning (DL) is a type of ML that can use pixels or voxels from bioimaging data as inputs to *neural network* models, which iteratively relate inputs to outputs in flexible models allowing complex nonlinear functions[83]. DL is well-suited for automating time-intensive tasks in imaging interpretation[84]. To train such an algorithm, images are used as inputs, and labeled segmentations are needed as outputs. The DL algorithm can then learn to automatically segment radiological images to identify potential pathologies. For example, large contemporary datasets (such as UK Biobank) provide vast amounts of imaging data, which are mostly present in "unlabeled" formats without phenotypic measures or annotation. Several groups have recently developed DL models to derive clinically relevant phenotypic data from these images[85-87]. In addition, DL algorithms can identify diabetic retinopathy from retinal images with a higher risk of vision loss in individuals with diabetes[88]. There are several potential challenges in developing effective DL algorithms for phenotypic characterization, however. These models may not

translate well from one sample/dataset to another, as even slight differences in image acquisition and quality may negatively impact model performance[89,90]. Furthermore, DL algorithms are statistical models that do not understand the underlying meaning of the inputted information. It is therefore conceivable that decisions are being made not based upon disease-related imaging abnormalities, but based on acquisition settings or other imaging features, such as markers on chest X-rays[91]. In addition, it is increasingly recognized that DL algorithms may perpetuate health inequities based on gender, race, ethnicity, or other factors if training data sets lack demographic diversity or if outcomes partially reflect underlying healthcare disparities[92].

Identification of abnormalities and novel imaging phenotypes

AI-derived outcomes may provide novel bioimaging phenotypes that are not apparent to the human eye through unbiased assessments of imaging characteristics or imaging data. For example, DL algorithms can extract complex information from low cost and widely available images such as chest X-rays that can be used to predict incident lung cancer or cardiovascular, respiratory, or lung cancer mortality[93,94]. *Radiomics* is a *feature-generative* technique that derives new imaging measures based on mathematical properties of the imaging data including intensity distribution, texture, and shape[95]. Radiomic analysis of coronary plaques may potentially improve prediction of cardiovascular events via detailed description of high-risk properties of atherosclerotic lesions[96,97]. Analysis of radiomic features describing texture properties of the myocardium on CMR images may enable detection of subtle differences in the myocardial intensity values to better distinguish patients with subacute and chronic myocardial infarction[98]. Radiomics features may also help to differentiate pathologies with similar gross appearance to the human eye, such as hypertensive heart disease and hypertrophic cardiomyopathy[99]. It is important to note that potential association of radiomic features with disease entities does not imply causation[90]. Connecting biological processes with specific radiomic features is, therefore, only speculative at present.

AI methods are being applied to CT images to develop novel disease classifications in COPD (**Figure 2**). For example, DL algorithms have been trained to classify emphysema on lung CT and scores derived from the DL algorithms can improve classification of emphysema and outcome prediction when compared to visual scoring[101]. Using these methods, investigators identified two distinct trajectories of emphysema progression: 1) airway→tissue type in which large airway abnormalities precede emphysema; and 2) tissue→airway type in which small airway dysfunction and emphysema antedate large airway wall abnormalities[102]. Unsupervised

ML methods have also been applied to define novel emphysema sub-phenotypes based upon texture and anatomical location of emphysema on lung CT scans[100].

Radiomics and DL-based imaging traits have been mostly evaluated in small pilot studies, thus far; larger scale observational studies[103], clinical trials, or innovative study designs such as *in silico* trials, are necessary to assess their superiority over traditional imaging measures for clinical applications.

D. EMERGING GENOMIC APPROACHES

The GWA era has yielded many important mechanistic insights and information regarding genetic variants associated with higher disease risk. However, several barriers to clinical translation of genomic findings are present currently. First, there remains substantial unexplained heritability for many common complex diseases of multifactorial etiology. Second, the underlying mechanisms linking genetic variants with imaging traits, and ultimately with disease states, is currently lacking for many SNVs[5]. Third, variable expressivity (penetrance) of genetic variation needs to be better understood through analysis of gene-gene and gene-environment interactions, and the variability of such interactions in the time domain over the lifecourse. Fourth, genetic determinants of bioimaging traits may vary based on racial/ethnic background and should be studied in diverse populations. Advances in the resolution of genetic sequencing and harnessing complementary multi-omic analyses have the potential to address these current challenges thereby broadening the impact of imaging genomics investigations.

Whole genome sequencing

The initial phases of GWA studies used genotyping arrays to directly ascertain 200,000–1 million genetic variants and then leveraged reference panels to impute a larger number of variants[11,12,14,22]. However, historical reference panels have important limitations including inadequate coverage of rare or private variants, difficulty identifying causal variants due to linkage disequilibrium blocks, and the potential for bias when non-European populations are less well represented in the derivation samples.

Whole genome sequencing (WGS) provides expanded coverage of the entire genome thereby overcoming the reliance on reference panels and imputation and enabling a balanced assessment across the genome. To harness WGS for genetic discovery, the National Heart, Lung, and Blood Institute initiated the large-scale WGS TOPMed (Trans-Omics for Precision Medicine) initiative (www.nhlbiwgs.org). TOPMed was established to advance genetic discovery by addressing some of the limitations of the European-ancestry centric, and array-based GWA

studies conducted previously. Over 80 existing studies with phenotypic data are part of TOPMed. Across these studies, TOPMed has generated WGS data on over 181,000 participants, at an average sequencing depth of 38x. Ethnic and racial diversity is a priority in TOPMed with 40% participants of European ancestry, 31% of African ancestry, 15% of Hispanic ancestry, and 9% of Asian ancestry.

Data on the first 53,831 participants with available sequencing data in TOPMed were recently reported[104]. In this subsample, 410 million genetic variants were identified, of which 97% had a minor allele frequency below 1%. In fact, 46% appeared only in a single individual ('singletons'). When this dataset was used as a reference panel for genotype imputation, the variants with minor allele frequencies as low as 0.01% were imputed with high quality (r^2 >0.9) in individuals of both European and African ancestry allowing the inclusion of much rarer variants in GWA studies than was possible with previous reference panels. The inclusion of participants from multiple ancestry groups leads to a substantial reduction in the size of linkage disequilibrium blocks at most loci (i.e., trans-ancestry fine-mapping) enhancing the ability to identify causal variants within large blocks of the genome with relatively high linkage disequilibrium in certain populations[105] (NHLBI TOPMed imputation server can be found at https://imputation.biodatacatalyst.nhlbi.nih.gov/).

With resources available through TOPMed, WGS data can be combined with high quality complementary "omics" data (including epigenetics, transcripts, metabolites, and proteins) and detailed phenotypic information (available phenotypic data can be found at https://biodatacatalyst.nhlbi.nih.gov). Numerous studies included in TOPMed have heart and lung imaging phenotypes including CAC, echocardiograms, CT, and MRI. GWA studies leveraging WGS are now underway and are expected to identify variants that are not well covered by standard imputation approaches such as rare variants, variants on the X chromosome, and variants restricted to non-European populations, providing the potential for discovery of novel disease-causing variants.

Trans-omic signatures of imaging traits

High-dimensional molecular data (e.g., transcriptomics, proteomics, metabolomics) can provide complementary information to genetic studies for identifying mechanisms of disease related to imaging phenotypes. These tools can be used to better understand the downstream implications of genetic variants, to improve the precision of CVD phenotyping by defining endophenotypes that can be correlated with imaging traits, or to identify novel disease-associated biological pathways for mechanistic investigations[106]. Importantly, molecular

signatures may reflect causal links between genetic variation and clinically relevant phenotypes (such as bioimaging traits), but they also might represent compensatory mechanisms or epiphenomena associated with both the genetic variant and the phenotype, but without a causal relation. Thus, an integrative trans-omic approach that assimilates data across profiling platforms will be the ideal approach to elucidate the potential roles of different molecular signatures in disease pathogenesis. Herein, we discuss investigations using proteomic and metabolomic data to examine molecular signatures of adverse cardiac structural remodeling traits as examples of how high-dimensional data derived from different profiling methods may be used to complement imaging genomics analyses[107].

High-throughput proteomic and metabolomic data and imaging phenotypes

Numerous proteins have been associated with imaging signs of cardiac remodeling and with heart failure risk in prior studies assessing a limited set of candidate proteins[108]. Technological advances in high-throughput proteomic profiling platforms now enable deep and relatively unbiased profiling of more than 5000 of the ≈20,000 human proteins[109], which can provide a broader view of the relations of the circulating proteome with cardiac imaging traits. For example, proteomic signatures of coronary flow reserve can be identified in peripheral blood[110]. Such a molecular signature can be used as a discrete disease phenotype for other analyses (such as genetic discovery) or to uncover biological pathways relevant to heart failure pathobiology. Proteomic profiling has also been used to evaluate how inflammatory pathways may mediate the association of general comorbidity and echocardiographic traits in patients with heart failure with preserved ejection fraction[111]. A discovery platform comprising ≈1300 plasma proteins was used to identify novel associations of proteins representing different biological pathways with echocardiographic traits[112].

Hundreds of small molecule metabolites can also be measured from the blood using nuclear magnetic resonance- or mass spectrometry-based techniques[113]. Heart failure and its imaging correlates represent attractive conditions for metabolomic analysis as the failing heart undergoes extensive metabolic remodeling with reduced fatty acid oxidation and a shift to using glucose as its primary fuel source[114]. The reduction in fatty acid oxidation is reflected by increased circulating levels of long-chain acylcarnitines[115]. In individuals with aortic stenosis, long-chain acylcarnitines are present in higher levels in blood in those with adverse cardiac remodeling phenotypes, such as severe left ventricular hypertrophy and reduced LV systolic function[116]. Within 24 hours after aortic valve replacement, a drop in circulating long-chain acylcarnitine concentrations can be observed, demonstrating changes in cardiac metabolism

that precede detectable changes in cardiac structure or function[116]. Additional metabolites, such as lipid ceramides[117], kynurenine (a tryptophan derivative implicated in vasodilation), and aminoadipate are also associated with cardiac structure and function[118]. Metabolite profiling, therefore, can identify signatures in circulating blood that correspond to molecular abnormalities in the heart itself; these abnormal metabolite profiles relate to imaging measures of heart structure and function and may predict future heart failure. It can be a challenge, however, to decipher whether these molecular signatures are causal in the disease process. Leveraging longitudinal molecular data in carefully phenotyped individuals before the onset of manifest heart or lung disease will be an important tool to elucidate which molecular profiles or pathways might play causal roles.

Correlating circulating protein and metabolite concentrations with genetic determinants

Circulating protein and metabolite concentrations are partly heritable, with a relatively large amount of their variation explained by genetic factors[119-121]. Protein or metabolite levels that are related to imaging traits can be associated, therefore, with genetic variation (i.e., protein quantitative trait loci [pQTLs] or metabolomic quantitative trait loci [mQTLs]) to discover new genetic markers of disease risk[120]. The statistical technique of *Mendelian randomization* can provide data in support of a causal role for a protein or metabolite in disease pathogenesis by leveraging the random allocation of pQTLs/mQTLs among individuals[122]. Genetic determinants of protein/metabolite levels can also be used to "replicate" findings from proteomic and metabolomic analyses in external cohorts by using their quantitative trait loci as proxies for the level of the molecule itself[112,123]. This approach was recently used to *replicate* relations of novel proteins with echocardiographic traits from one community-based sample in a large, international, genetic consortium[112]. Alternatively, metabolomic and proteomic profiles can be used to better understand the molecular mediators of the associations of genetic variants with clinical traits[107,124].

E. METHODOLOGICAL DEVELOPMENTS IN IMAGING GENOMICS

Imaging genomics involves analysis of high-dimensional data sources and, therefore, poses challenges for standard data analysis and computing techniques. In the following section, we provide an overview of methodological developments in computational strategies and bioinformatics approaches aimed at harnessing massive datasets for imaging genomics analysis.

Computational strategies for heritability and genetic association studies

The standard statistical genetics model for both heritability and association studies becomes computationally impractical when applied in large-scale imaging genetic studies. Through algorithmic and hardware acceleration approaches, the computational burden can be reduced from $10^{10\text{-}12}$ to $10^{1\text{-}2}$ hours.

Algorithmic acceleration of the standard genetic model

For imaging genomics studies, a relevant model needs to be evaluated for every imaging trait and every genetic polymorphism. A typical voxel-wise MRI/CT analysis may involve several hundred thousand traits each detailing regional information. These analyses require maximizations of likelihood for each of the voxel-wise traits and can each take between 10-50 iterations. Therefore, a GWA of 1,000,000 SNVs and 100,000 voxels would require 10^{11} maximizations of likelihood. Each iteration of the likelihood algorithm requires the inversion of the covariance matrix, which is a substantial computational effort that grows as $N^{2\text{-}3}$ with increasing sample size (N) and becomes impractical for large-scale imaging genomics efforts.

Algorithmic acceleration of the standard genetic model can provide substantial improvements in the efficiency of conducting large-scale imaging genomics analyses[125-127]. This is accomplished by reducing the computational effort associated with the inversion of the covariance matrix for each likelihood calculation. The eigen value decomposition approach performs an orthogonal transformation to diagonalize the covariance matrix, thereby making the matrix inversion computationally trivial[128]. To reduce the iterative burden of maximum likelihood estimates, a two-step ordinary linear squares followed by a weighted linear squares approximation (*Fast and Powerful Heritability Inference* [FPHI]) can be used to solve the maximum likelihood estimation non-iteratively[125]. The FPHI model can then be expanded to a *Fast and Powerful Genome-wide Association* (FGPA) for genotype association analysis of the full model including measured SNVs[126]. Additional computational performance can be achieved by testing the statistical significance of association using the Wald test (FPGA-Wald). Hence, the algorithmic approximation of standard genetic models using FPHI, FPGA and FPGA-Wald, provides significant improvement in computational efficiency versus classical approaches, reducing the computational complexity from $N^{2\text{-}3}$ to N^{1}. Detailed discussion of these acceleration approaches is included in the **Supplemental Material**.

Hardware acceleration of imaging genomics computations

Even with the algorithmic approximations discussed above, the computational burden of large-scale imaging genomics studies is immense and calls for efficient implementation using modern hardware. Computational clusters are built of nodes equipped with central processing and graphics processing units (CPU/GPU) offering multiple computational cores (typically 2-64 for CPUs and 1000-8000 for GPU). The CPU and GPU version of FPHI and FPGA can be implemented using linear algebra software libraries that optimize the code for parallel scientific computing in a CPU and GPU environment (OpenMP; https://www.openmp.org). FPHI and FPGA algorithms are coded using cuBLAS (https://developer.nvidia.com/cublas) linear algebra libraries for GPU computing. More information is available in the **Supplemental Material**. All algorithmic, software, and hardware approaches discussed above are implemented in the solar-eclipse software (http://www.solar-eclipse-genetics.org/) and are freely available for download, use, and distribution.

Bioinformatics strategies for imaging genomics studies

Given the high dimensionality of both imaging and genomics data, massive univariate analysis methods (i.e., single imaging trait vs. single variants) face a huge burden for multiple statistical testing correction, which results in reduced detection power. Various bioinformatics strategies can be used to reduce the multiple hypothesis testing burden and to improve the interpretability and mechanistic insight gained from imaging genomics investigations.

Meta- and mega-analysis

Meta- and mega-analyses can be used to boost the statistical power of imaging genomics analyses by creating massive datasets. In meta-analysis, summary data from many collaborating cohorts can be combined after overcoming logistical and regulatory challenges in merging participant-level data[22]. In mega-analysis, participant-level data on many individuals are centrally analyzed.

Polygenic and multivariate analysis

Another strategy to improve detection power is to leverage associations involving multiple imaging or genomic markers, thereby reducing the effective number of tests performed. By combining SNVs or imaging traits into statistically or biologically related groups, these techniques may also help deconvolute mechanistic complexity and lead to better understanding of disease subtypes.

Polygenic risk scores (PRS) can capture the accumulated effect from a set of trait-related SNVs[129]. While each SNV may not have a statistically significant effect on the trait, the collective effect captured by the PRS may explain a considerable portion of the trait variance. By examining a PRS instead of many individual SNVs, the burden for multiple hypothesis testing correction is reduced. Other methods can be used to investigate associations involving multiple genomic markers, such as multiple regression to examine the joint effect of several SNVs (chosen based on prior knowledge) on each imaging trait[130]. Gene-based GWA can estimate the aggregate effect of all the SNVs within each gene on each imaging trait[131]. Commonly used techniques for multi-trait analysis include: 1) combining single-trait results (e.g., selecting the SNV with the minimum p-value[132]); 2) applying univariate analysis on a small number of extracted trait features (e.g., the average trait or first few components from principal components analysis[133]); and 3) classical multivariate analysis methods such as multivariate analysis of variance (MANOVA[134]) and generalized least squares regression[135].

Pathway and network enrichment analysis

Enrichment analysis organizes data into sets based on functional pathways and networks, thereby providing natural connections to biological mechanisms. There are two standard types of methods for enrichment analysis: 1) *threshold-based* methods (e.g., hypergeometric test or Fisher's exact test) are designed to identify pathways or networks over-represented by GWA hits; and 2) *rank-based* methods (e.g., GSEA-SNP[136]), which employ a Kolmogorov-Smirnov-like running sum to quantify the degree to which a gene set is over-represented at the top of the gene list ranked by the GWA results. Similarly, network-based GWA studies can identify functional modules from biological networks that are enriched for top GWA findings[137]. Most existing methods analyze tissue-free networks without reflecting phenotypic specificity, but novel tissue-specific functional interaction networks are being developed[138].

Regularized regression and correlation analyses

Regularized regression models[139,140] and bi-multivariate correlation models, such as sparse canonical correlation analysis (SCCA)[141,142], can be used to examine multi-SNV-multi-trait associations. These models often include a sparsity-inducing regularization term to identify a smaller number of relevant imaging and genomic markers and to minimize overfitting[139,140]. Regularized regression and SCCA models benefit from relative ease of interpretation.

Outcome prediction and joint association learning and outcome prediction

Another challenge in imaging genomics is integration of imaging and genomics data for improved prediction of clinical outcomes. The most straightforward methods are to concatenate imaging and genomic data together, and then apply conventional predictive models[143]. Advanced ML and DL methods are also being developed to co-relate genetic and imaging markers with relevant outcomes[144,145]. ML models can also be used for joint exploration of the associations among genomics, imaging traits, and outcome[146].

F. RESEARCH OPPORTUNITIES AND PRIORITIES (Summarized in **Table 2)**

Increased availability of imaging genomics data in diverse populations

While consortia and large biobanks with imaging and genomic data are proliferating, initial datasets mostly comprised white individuals of European descent. Multiethnic large samples to capture the diversity and spectrum of phenotypic variation are required for the benefits of imaging genomic findings to be shared equally across populations. TOPMed and the Million Veterans Program[147] have both sought to enroll racially diverse samples and efforts to leverage and expand the available imaging phenotypes within these initiatives and in new cohorts should maintain the important focus on establishing representative study samples with diversity of race, ethnicity, age, and sex, among other factors.

Data harmonization and infrastructure

The unprecedented scale, complexity, and heterogeneity of multidimensional big datasets available to the research community (including genetics, multi-omics, bioimaging, electronic health record data) requires effective data integration and harmonization methods to realize the full potential of these invaluable resources. Tools are being developed in partnerships with NIH Data Commons[148] and NHLBI BioData Catalyst[149] to leverage cloud-computing resources for sharing and analyzing TOPMed and imaging datasets within a secure cloud environment. Unifying imaging biomarkers and genomic data requires the availability of imaging data in formats that can be shared efficiently and securely. These efforts would, therefore, benefit from efficient and scalable computational infrastructure to facilitate different types of large-scale collaborations across cohorts (e.g., cloud computing for teams working with one single centralized data repository) and federated learning for teams working with distributed data sets.

Centralization of efforts around specific disease areas

Translating imaging genomics findings from the initial discovery of SNV-imaging trait associations to the use for clinical risk prediction or mechanistic insight requires coordinated efforts across disciplines. This may require large, diverse datasets for the initial discovery of genetic variants, replication in other populations, complementary molecular phenotyping through gene expression, metabolite profiling, or proteomic investigations, and functional and mechanistic studies harnessing robust model systems. Integration of these complex steps would be facilitated by centralized "nodes" of interdisciplinary investigators centered around disease areas or pathophysiologic processes (e.g., inflammation or fibrosis). These centralized efforts will also facilitate the development of standards for imaging genomics methods and related interpretations norms.

Methodological advances in imaging genomics

Despite the tremendous progress made in recent years in the field of imaging genomics and the development of necessary tools for its implementation, substantial methodological challenges remain. Statistical and computational tools to integrate these high-dimensional data sources are available, but they are variable across different fields and standardized methods and interpretation norms are not yet established. These analyses have been largely conducted to discover statistical associations; leveraging longitudinal measures and more advanced statistical techniques may enable causal inferences regarding the genetic etiologies of imaging traits.

Dedicated focus on less common conditions

Most consortia for imaging genomics analyses have been formed to enhance statistical power to evaluate common variants with relatively low effect sizes. While efforts to better characterize and understand genetic underpinnings of common disease will undoubtedly continue, consortia should also be formed to study genetic correlates of imaging traits in less common diseases. In many cases, while the manifest disease itself may be relatively rare, imaging features of its pathogenesis can be detected years earlier and in a broader population (such as aortic calcification for aortic stenosis or ILAs for IPF). By centralizing efforts to study less common diseases, investigators may identify pathophysiological mechanisms that are applicable to other disease forms as well.

F. SUMMARY

The emerging field of imaging genomics seeks to combine state-of-the-art imaging techniques with genomic information to understand the genomic architecture of bioimaging traits. Several common heart and lung diseases (e.g., atherosclerosis, COPD) are caused by a combination of environmental and genetic factors, rendering imaging genomics an especially powerful tool for improving the precision with which they are characterized across the lifecourse. Measuring precise bioimaging phenotypes with relevance to clinical disease and elucidating their genomic contributors can improve understanding of disease pathogenesis, identify relevant biological pathways, lead to the discovery of novel therapeutic targets, and facilitate disease prevention characterized by more precise risk prediction and screening and enhanced opportunities for prevention of clinically meaningful events.

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Supplemental Material: Additional Information on Algorithmic and Computational Acceleration of Standard Genetic Models for Imaging Genomics Analyses

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FIGURE LEGENDS

Figure 1. Imaging genomics: learning problems, applications, and statistical and machine learning considerations. Adapted from reference[6]. The key learning problems (or objectives) of imaging genomics are displayed in panel (a). Panel (b) displays potential applications for combining biomedical imaging and state-of-the-art genomics information for disease characterization, diagnosis, and risk prediction. Considerations for machine learning and statistical approaches to imaging genomics analyses are shown in panel (c).
Abbreviations: GWA, genome-wide association; WGS, whole genome sequencing; Dz, disease; surv, survival; dysf, dysfunction; mod, moderate

Figure 2. Novel imaging-based sub-phenotypes of COPD and emphysema. (Reproduced with permission from reference[100].) Spatially-informed lung texture patterns (sLTPs) were derived using unsupervised clustering on chest CT scans from 317 participants in the MESA COPD study based on the texture and spatial location of hundreds of regions-of-interest per scan. Panel (a) shows two examples of lung CTs and colorized maps of their different sLTPs. Panel (b) displays characteristics of the 12 lung texture patterns based on axial cuts from nine random regions of interest (top of each box), the average lung texture pattern calculated from the images (middle of each box), and the spatial density plots (bottom of each box). These lung texture patterns are reproducible and relate to measures of symptom and disease severity.
Abbreviations: sLTP=spatially-informed lung texture patterns; S=superior; I=inferior; P=posterior; A=anterior

Table 1. **Bioimaging modalities for heart and lung diseases**

Imaging modality	Characteristics	Examples of applications in heart and lung diseases
Computed tomography (CT)	-Fast, relatively low radiation dose -Excellent spatial resolution -High throughput, widely available	*Heart:* -Coronary artery and aortic valve calcium (no contrast required) -Coronary artery angiography (with contrast) *Lungs:* -Qualitative disease characterization (i.e., emphysema, ILD) -Quantitative lung measures (e.g., airway wall thickness, interstitial abnormalities, small vessel pruning)
Magnetic resonance imaging (MRI)	-Provides simultaneous assessment of heart structure and function -Evaluation of lung parenchyma with traditional methods is challenging due to low signal intensity -Takes longer than CT, but can be performed efficiently in large cohorts -No radiation required	*Heart:* -Cardiac structure and function (e.g., chamber sizes, ejection fraction) -Fibrosis, iron deposition, presence of scar through specialized sequences *Lung:* -Pulmonary vascular characteristics -Methods in development for lung parenchyma evaluation including different signal sequences and inhalation of gas mixtures serving as contrast agents
Ultrasound (echocardiography)	-Easily obtained and readily available -Radiation free -Excellent characterization of heart structure and function	*Heart:* -Cardiac chamber size measurement -Cardiac function, including quantitative measures such as strain imaging
Molecular imaging	-Precise biological characterization -Can measure disease *activity*, not just organ structure/function -May allow disease identification prior to overt manifestations -Relatively low throughput, challenges with obtaining images at large scale -Higher radiation dose necessary -Largely preclinical	*Heart:* -Atherosclerotic plaque activity with 18F-FDG PET imaging -Microvascular calcification with 18F-fluoride PET tracer -Assessment of myocardial perfusion and metabolism with PET *Lung:* -Different probes can identify steps in development of lung fibrosis including collagen deposition and cross-linking, fibrosis development, fibroblast activity, and inflammation

Abbreviations: ILD, interstitial lung disease; FDG, fluorodeoxyglucose; PET, positron emission tomography

Table 2. Research priorities in imaging genomics

Research Priorities
Methods development in imaging, genomics, and their statistical integration
Infrastructure for data analyses and data sharing
Multiethnic large samples to capture diversity and spectrum of phenotypic and genomic variation of common conditions
Analysis of longitudinal imaging data in relation to longitudinal molecular data
Methods development for testing effect modification and causal inference adapted to imaging genomics
Consortia focused on less common heritable conditions
Defining standards for imaging genomics methods and interpretation norms

Figure 1.

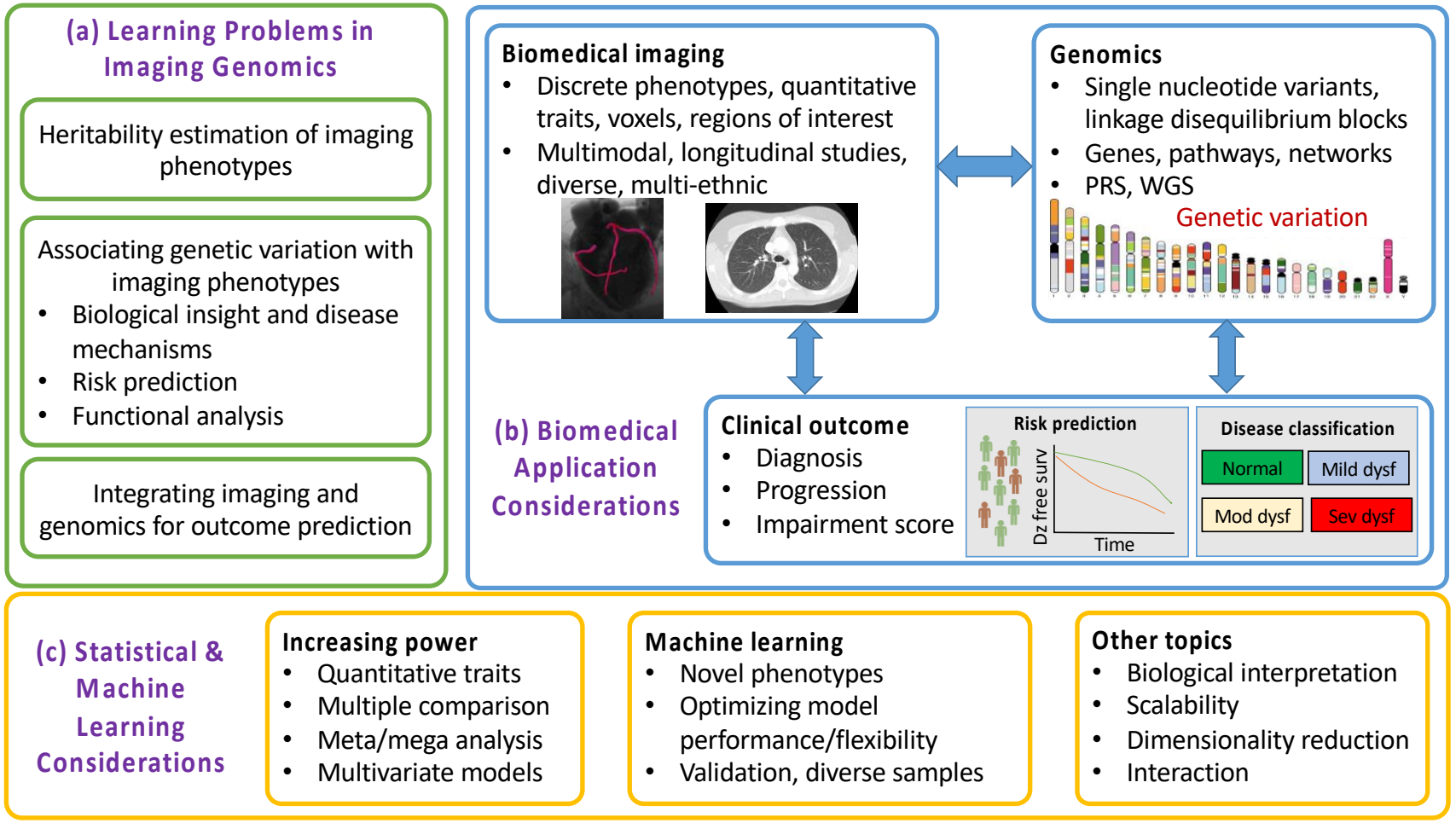
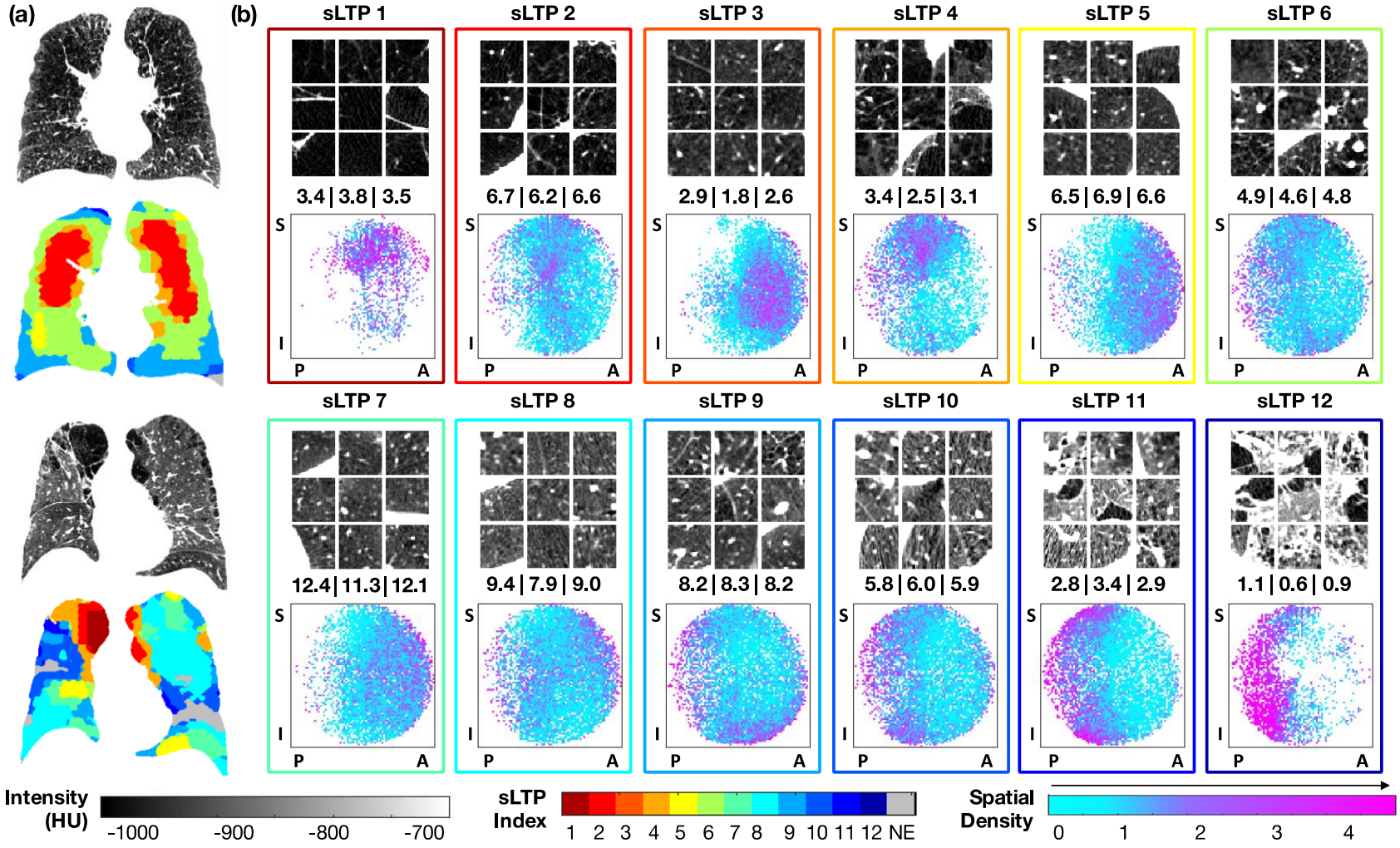

(a) Learning Problems in Imaging Genomics
Heritability estimation of imaging phenotypes
Associating genetic variation with imaging phenotypes
• Biological insight and disease mechanisms
• Risk prediction
• Functional analysis
Integrating imaging and genomics for outcome prediction
Biomedical imaging
• Discrete phenotypes, quantitative traits, voxels, regions of interest
• Multimodal, longitudinal studies, diverse, multi-ethnic
Genomics
• Single nucleotide variants, linkage disequilibrium blocks
• Genes, pathways, networks
• PRS, WGS
Genetic variation
(b) Biomedical Application Considerations
Clinical outcome
• Diagnosis
• Progression
• Impairment score
Risk prediction
Dz free surv
Time
Disease classification
Normal
Mild dysf
Mod dysf
Sev dysf
(c) Statistical & Machine Learning Considerations
Increasing power
• Quantitative traits
• Multiple comparison
• Meta/mega analysis
• Multivariate models
Machine learning
• Novel phenotypes
• Optimizing model performance/flexibility
• Validation, diverse samples
Other topics
• Biological interpretation
• Scalability
• Dimensionality reduction
• Interaction

Figure 2.


(a)
(b)
sLTP 1
sLTP 2
sLTP 3
sLTP 4
sLTP 5
sLTP 6
3.4 | 3.8 | 3.5
6.7 | 6.2 | 6.6
2.9 | 1.8 | 2.6
3.4 | 2.5 | 3.1
6.5 | 6.9 | 6.6
4.9 | 4.6 | 4.8
sLTP 7
sLTP 8
sLTP 9
sLTP 10
sLTP 11
sLTP 12
12.4 | 11.3 | 12.1
9.4 | 7.9 | 9.0
8.2 | 8.3 | 8.2
5.8 | 6.0 | 5.9
2.8 | 3.4 | 2.9
1.1 | 0.6 | 0.9
S
I
P
A
Intensity (HU)
-1000
-900
-800
-700
sLTP Index
1 2 3 4 5 6 7 8 9 10 11 12 NE
Spatial Density
0 1 2 3 4