Systematic Review on glaucoma detection using generative adversarial networks: Coherent Taxonomy, Motivations, Open Challenges, Recommendations and New Research Direction in the emerging Covid19 pandemic

Ali Q. Saeed, Siti Norul Huda Sheikh Abdullah, Jemaima Che-Hamzah, Ahmad Tarmizi Abdul Ghani

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Abstract

Background: Glaucoma means irreversible blindness. Globally, it is the second retinal disease leading to blindness, just preceded by the cataract. Therefore, there is a great need to avoid the silent growth of such disease using the recently developed Generative Adversarial Networks(GANs).

Objective: This paper aims to introduce GAN technology for the diagnosis of eye disorders, particularly glaucoma. This paper illustrates deep adversarial learning as a potential diagnostic tool and the challenges involved in its implementation. This study describes and analyzes many of the pitfalls and problems that researchers will need to overcome in order to implement this kind of technology.

Methods: To organize this review comprehensively, we used the keywords: ("Glaucoma", "optic disc", "blood vessels") and ("receptive field", "loss function", "GAN", "Generative Adversarial Network", "Deep learning", "CNN", "convolutional neural network" OR encoder), in different variations to gather all the relevant articles from five highly reputed databases: IEEE Xplore, Web of Science, Scopus, Science Direct, and Pubmed. These libraries broadly cover technical and medical literature. For the latest five years of publications, we only included those within that period. Researchers who used OCT or visual fields in their work were excluded. However, papers that used 2D images were included. A large-scale systematic analysis was performed, then a summary was generated. The study was conducted between March 2020 and November 2020.

Results: We found 59 articles after a comprehensive survey of the literature. Among 59 articles, 29 present actual attempts to synthesize images and provide accurate segmentation/classification using single/multiple landmarks or share certain experiences. Twenty-nine journal articles discuss recent advances in generative adversarial networks, practical experiments, and analytical studies of retinal disease.

Conclusions: Recent deep learning technique, namely generative adversarial network, has shown encouraging retinal disease detection performance. Although this methodology involves an extensive computing budget and optimization process, it saturates the greedy nature of deep learning techniques by synthesizing images and solves major medical issues. There is no existing systematic review paper on retinal disease utilizing generative adversarial networks to the extent of our knowledge. Two paper sets were reported; the first involves surveys on the recent development of GANs or overviews of papers reported in the literature applying machine learning techniques on retinal diseases. While in the second group, researchers have sought to establish and enhance the detection process through generating as real as possible synthetic images with the assistance of GANs. This paper contributes to this research field by offering a thorough analysis of existing works, highlighting current limitations,

and suggesting alternatives to support other researchers and participants to improve further and strengthen future work. Finally, the new directions of this research have been identified.

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Keywords: Glaucoma; Generative adversarial network; Deep learning; Systematic literature review; Retinal disease; Blood vessels; Optic Disc

Introduction

Blindness and visual impairments often result from cataracts, age-related macular degeneration, and glaucoma[1,2]. Glaucoma is a neurodegenerative disease that damages the optic nerve and causes visual field loss[3]. As it is an asymptomatic disease, it is known as the silent thief of sight[4], patients unaware of the infection until irreversibly vision impaired, Affected individuals are 50% ignorant of the disorder[5–7]. Early phases of glaucoma have no symptoms or visual field changes[8]. As the disease progresses, a slow narrowing of the visual field can occur. If left untreated, glaucoma may contribute to total blindness[9]. Loss of vision usually begins on the eye's side then approaches into the middle.

Statistically, Glaucoma affects millions of people globally, with more than 64 million cases recorded in 2013, and other studies estimated 76 million by 2020 and 111.5 million by 2040[9,10]. Glaucoma is the second leading cause of blindness worldwide, preceded by cataracts, and impacts 4.5 million individuals[9,11], more than 10% of the gross burden population[10]. Owing to its asymptotic function, about 70% of the glaucoma sufferers are unaware of the illness's existence[12,13] in the early stage. Thus, we need to provide early detection and evaluation. Then, a more effective follow-up takes place since a cure can slow down the transmitting disease[8].

Cataracts may be reversed by surgery, while glaucoma causes lifelong blindness. Elevated intraocular pressure (IOP) is the most common cause of glaucoma. The Tonometer measures IOP. But IOP is not always an accurate and adequate indicator of glaucoma, since glaucoma would not always cause a rise in IOP[14], rather deterioration of Optic Nerve head (ONH) does. Visual information flows through the ONH to the brain. ONH consists of a bright spherical area called the optic disc (OD), and a wider circle-like area called the optic cup (OC). Figure 1 shows the structure of ocular images.

An ONH assessment distinguishes regular vs. glaucomatous cases through a manual calculation of ONH geometric structures. Measurements such as Cup-to-Disc Ratio (CDR), ISNT rule, disc diameter, and rim area are recommended as diagnostic features for glaucoma screening[15–17]. Among them, the CDR is a reliable therapeutic feature for early glaucoma screening and diagnosis[18,19]. Each of the derived CDR parameters (diameter or area) is the ratio between the OC and the OD. CDR values rise when illness progresses and become higher than about 0.6–0.7 as the patient has a stronger chance of developing glaucoma[20].

Based on[21], a CDR of at least 0.65 is deemed glaucomatous in clinical practice. The CDR score tracks the development of glaucoma over time, effectively screening the condition early[22]. However, manual assessing each cup and disk is labor-intensive and often time-consuming. The examiner must be expert and qualified to assess these features.

Nowadays, Deep Learning Methods(DLMs) has been an active research field that can learn to generate extremely complex features from input data automatically. In 2014, a new deep learning architecture proposed by[23], which belongs to the family of unsupervised learning algorithms that have proved their merits in generating synthetic images and solving the problems of image-to-image translation in natural domain[24,25].

Originally, GANs consist of two neural networks, the generation network(G) and the discriminator network (D), plus a noise vector(z) sampled from a known distribution, which is used to generate (fake samples) data points, see figure 2. The basic idea of this technique is to let these two networks compete against each other until they reach a convergence point. The role of the generator is to generate samples as close to real images as possible to fool the discriminator, while the discriminator is trying to distinguish the generated images out from the real ones. As a result, G generates outputs with a distribution very close to real data distribution[26–28]. Different types of GAN have been proposed through the continuous improvement of the original GAN's theory. GAN gradually showed its extraordinary charms and started to shine brilliantly in various application fields such as[24,29,30].

To date, several review articles summarizing the technology of deep learning in Ophthalmology have been published[17,31–34]. Nevertheless, none of them have focused on the emerging breaking through the technique of GANs using fundus photographs. In this paper, we aim to elucidate research efforts such as those GANs' architectures mentioned earlier that have taken place in response to the new and disruptive technology, mapping the research landscape from literature onto a coherent taxonomy of the key features that characterize such emerging line of research. Additionally, future works of this research will be proposed and described in detail.

Methods

Information sources

Guided by[35], we conducted a comprehensive search to find all GANs-based articles related to glaucoma by searching the best and most reliable libraries.: 1)Scopus, 2)Science Direct, 3)IEEE Xplore, 4)Web of Science (WoS), and 5)PubMed Center(PMC). This collection includes technical and medical literature, perfectly reflecting all research activities in this discipline.

Procedure of study selection

The method for choosing appropriate studies was on the basis of two stages, screening and filtering. Successively, both stages met the same criterion for inclusion and exclusion. Both duplicates and unrelated studies by title and abstract skimming were omitted during the first stage. Then the result in a set of papers was entirely read, analyzed, and summarized in the filtration stage.

Search

This work was carried out between March/2020 and November/2020. On the basis of highly reputable libraries (IEEE Xplore, Science Direct, PubMed, Scopus and WoS) with various keyword combinations used in the search process. A mixture of keywords was used to describe our scope of study containing the words: \glaucoma," \optic disk," \blood vessels and \receptive field," \loss function," \GAN," \generative adversarial network," \ deep learning," \convolutional neural network," \ CNN," \ Encoder," in different variations connected with the operator \OR".

The quest focused on different journals and conferences and omitted books and all other forms of study. Therefore we mainly concentrated on up-to-date and applicable scientific works relating to GANs publications in retinal disease, especially glaucoma. Figure 4 shows the exact query statement with the exclusion and inclusion criteria.

The validity of the collected papers (Scope Validation)

The total numbers of keywords in our collected papers are 115. To verify our research scope's validity, we analyzed these keywords and categorized them according to their co-occurrences. Then we set a threshold indicating the co-occurrences of each keyword across all over the papers. Let k=3 where k is a threshold. As a result, we got 15 keywords out of 115 that met the threshold. That is, each of these 15 keywords occurred at least three times in all of our collected papers.

Figure 3 illustrates the connection of each of these 15 keywords to each other. The circle's size indicates how frequently a single keyword has occurred. The more frequently co-occurrence keyword, the bigger circle size it gets, e.g., deep learning keyword is the biggest circle in the diagram, which indicates the most frequently occurring keywords in the collected papers. Another factor is the colour, which indicates how often a single keyword occurred per year wise.
From table 1, we noticed that the most frequently occurring keyword is deep learning, which is 20 times occurring beside its total links to other keywords is 27 times. Generative Adversarial Networks(GAN) occurred 17 times, with eighteen connections to other keywords, and the term glaucoma occurred eight times with twelve connections to other keywords. Therefore, we empirically demonstrated the validity of our search string used during the collection of our papers. As we can see in diagram 1, our research's scope is revolving around those three main keywords (the biggest circles) as they achieved the highest occurrence scores.

	Keywords	Occurrences	Total link strength
Techniques			
	Deep Learning	*20*	*27*
	Generative Adversarial Network(s) / GAN	*17*	*18*
	Artificial intelligence	3	8
	Machine learning	3	8
Diseases			
	Glaucoma	*8*	*12*
	Diabetic retinopathy	3	6
Imaging			
	Fundus image	3	6
	Medical imaging	4	5
Papers' contribution			
	Adversarial learning	3	4
	Optic disc segmentation	3	6
	Retinal vessel segmentation	3	4
	Generative models	3	3
	Retinal image synthesis	3	3

Table 1 Keywords occurrence

Inclusion and exclusion criteria

In this section, papers that meet the criteria in figure 4 were included. We taxonomize the included papers on a general and in-depth diagram consisting of two paper groups, namely the development studies group and reviews and surveys group. Papers in the first group were classified according to eight consecutive layers. In literature, researchers classified GANs into two to four categories; these categories were separately used by different researchers, as referenced accordingly in the points below. However, in our taxonomy, we combined them all. Furthermore, we added four more classification criteria as follows:

1. Method's architecture(Direct, Hierarchical, Iterative)[36];
2. Model's structure (Two players, Multiple players)[37];
3. GANs' category (Optimization function, Structure and conditional)[38–40] ;
4. Generator's backbone (U-net based or CNN-Based)[41];

Further, we added four more categories as the following:

5. Type of GAN used in a paper(VGAN, DCGAN, cGAN, CycleGAN),
6. Discriminator's receptive field(PixelGAN, PatchGAN, ImageGAN);
7. Landmarks used during the segmentation/classification process(single, multiple);
8. Paper's contribution(segmentation, classification, image synthesizing, mixed).

The exclusion criteria followed in this paper are: 1)Machine learning approaches, 2) 3D-based imaging (optical coherence tomography(OCT)), 3)Between classes papers, 4)out of scope papers.

Data collection process

All papers from different sources were summarized and saved in a single spreadsheet file for simplicity and a quick review. Significant remarks and comments were illustrated by full-text reading in our analysis scope and classification stage, which further refined our taxonomy. Needless to say, using the Mendeley application made hard-work simple as it provides the facilities to highlight, write comments, productive search prosperity, and most interestingly, set tags on closely connected paragraphs or posts; all these features could be accomplished inside the document itself or in the whole library. Finally, our results were summarized on an excel sheet and listed as tabular. The additional data set includes a list of articles, publishing source, articles' abstracts and contributions, the tools used in papers, audiences, objectives, architecture-based categorization table, and a list of relevant figures.

Results

The cumulative number of articles in the original search process is 455. 80% of the findings released between 2018-2021 and 20% between 2015-2017, distributed as follows: 15 papers from IEEE Xplore, 86 from Web of Science, 138 from Scopus, 147 from PubMed, and 69 from ScienceDirect. About 62 papers have been duplicated across the five databases.

Later, 318 papers (not GAN-based) were omitted after skimming the articles' title and abstract, leaving 75 papers. Further screening via full-text reading was carried out to reach the final number of publications with 59 articles after the 16 non-relevant papers were excluded. Comprehensive reading was performed on the 61 papers to create a general map to study this new emerging methodology.

Out of 59 papers, 30 (50.84%) focused on different GAN creation and real attempts to improve the efficiency of the architecture to better improve segmentation/classification precision, especially at an early stage of the disease with fewer false positives/negatives. Twenty-nine (49.15%) publications composed of general reviews and surveys relating either to GANs methods, its variants, recent GANs' applications, limitations, and potential prospect future, or reviews of retinal diseases, various DL detection methods, general analytical knowledge such as the dataset used the author's nationality contributed to these studies. From the above observation, we can best look through the literature, decide the general categories of our scope of the study, and boost literary taxonomy classification. Figure 5 describes the grouping of GAN-based approaches used in the literature according to their structure or optimization functions.

Reference[42] classifies GANs based on their architecture or the loss functions used to train the generator. It is worth noticing that the first four layers of our taxonomy have been separately used in other papers, therefore inspired by those studies, we used those categories together as a baseline for our taxonomy. We added other categories to classify brief literature work in depth according to 1) their discriminators (PixelGAN, PatchGAN, or ImageGAN), 2) a number of landmarks used in the segmentation or classification process (single landmark or multiple landmarks), 3) the backbone of GAN used in the article (e.g., DCGAN[43], Info-GAN[44], W-GAN[45], CGAN[24], Pix2pix[24], and Cycle-GAN[29]), and 4) the contribution of each paper (e.g., segmentation (s), classification (c) or synthesis (y)). In the following sections, we describe each category and provide some accompanying statistics.

Development studies category.

The first emerging of the GAN technique was in 2014 by[23]. Although researchers' continuous attempts to improve GANs performance in various ways like weights regularization, new loss functions, weights pruning and Nash equilibrium, it is still a new research field in deep learning techniques[42,46]. It is only recently this technique started to be adopted by researchers in the field of retinal disease, particularly glaucoma, roughly speaking at the beginning of 2018. Therefore the total set of papers that describe various experiments and tools used for detection or segmentation of the retinal image is 30/59 (50.84%) articles.

In this categories it is notable in figure 5, the first four layers classify articles based on the used method (direct, hierarchical or iterative)[36], model's structure[37], category of architecture (Optimization function or Structure and conditional)[38–40] and the generator's backbone (CNN-based or U-net based)[41] consecutively.

In the first layer, all the literature work followed the direct-based method. That means all the methods follow the philosophy of using one generator and one discriminator, and the structure of G and D is straight forward without any branch. None of the articles have used hierarchal or iterative methods; this reveals a new opportunity to the reader to a new direction of work using GANs in retinal disease to fill-in this literature gap.

The second layer classifies articles based on the number of players. Nearly 25/30 (83.33%) articles are two players, and only 5/30 (16.66%) articles are multiple players. In the latter, ref[47–49] are three player based methods, where both ref[48] and ref[49] frameworks consist of segmentation, generator, and discriminator networks. In ref[48], segmentation net and generator enlarge the training data set to improve the segmentation performance, while the discriminator solely focuses on identifying fake image-label pairs to ensure compatible utilities. However, in ref[49] the same architecture was used to synthesize images after performing traditional annotation-free methods to obtain coarse segmentations.

A slight difference in Ref[47] was performed, where Pathology-Aware Visualization Net has been used instead of the segmentation network, where both of Pathology-Aware Visualization and the generator were used to enhance the synthesized glaucoma images in specific pathological area, The synthesized image is re-enforced to provide a heat map close to the reference image input. The Patho-GAN can thus generate images of glaucoma fundus with clearer pathologies. In ref[50], the VGG19 network was incorporated with the three players to find the topology structure loss, combined with the other three losses (Adversarial loss, weighted cross-entropy, and Total variation loss) to be used by the generator. However, in[51], authors have used two encoders (E_s, E_t) where (s) is the source domain and (t) is the target domain; these Encoders were trained to impede the classification performance of the discriminators (D_+, D_-). In turn, these D+ and D- are trained to distinguish between positive/negative source images and positive/negative target images, and finally, a Classifier (C) tries to classify source/target images.

Following the references[38–40], we added the third layer to our taxonomy to classify papers either as a structure-based or an optimization-based method. The majority of studies 27/30 (90%) in this level are structure and conditional-based methods. While only 3/30 (10%) of studies, namely ref[26, 52] and[53], are optimization-based methods with two players structure, none of such methods has been recorded as multi-players based structure.

Some researchers tend to use objective function methods by updating specific loss functions or using a combination of losses to overcome the model collapse of GANs. This has happened when the generator keeps generating images with the same distribution or generating images with the same texture themes or color having marginal differences in human understanding[37]; for example, ref[26] have used least-squares loss function instead of sigmoid cross-entropy. Therefore, their experiment greatly improved the segmentation accuracy on both DRIVE and STARE datasets to force the generator to generate images with distribution close to real ones. In ref[52], the authors have used Wasserstein GAN-GP (WGAN-GP) to overcome the problem of instability training of the traditional GAN and generate accurate probability maps of blood vessels. WGAN-GP is an extension of WGAN; it uses gradient penalty instead of weight clipping to enforce the Lipschitz constraint. This type of GANs trains faster and generates higher quality samples than WGANs. Lastly, ref[53] proposed a framework for domain adaptation guided by Wasserstein-distance (WGAN) instead of typical adversarial methods for better stability training and convergence.

The subsequent layer in our taxonomy is to classify methods according to the generator's backbone (e.g., U-net based or CNN-based)[41]. Papers[25–27,54–63, 47,49,50] represent 50% of the studies, are U-Net based architecture. However another 50% of papers [25,28,67–72,48,51–53,59,64–66] are CNN-based generators.

Reference[25] is a very intensive study; authors have proposed multiple-channels-multiple-landmarks (MCML) as a new pre-processing framework. They used a combination of landmarks (vessel tree, optic disc, and optic cup images) to synthesize colored images with two types of GANs (Pix2pix and Cycle-GAN). Additionally, they have used Pix2pix architecture with two different generator's structures (e.g., u-net based and CNN based). They empirically demonstrated that the Pix2pix network with a ResUnet generator using high resolution paired images and MCML outperforms every single landmark-based GANs method regardless of their architectures. Furthermore, they were able to generate significant and realistic images.

The next distinguishing level in our taxonomy is the landmarks used in the papers. As figure 5 shows, references with red color have used single landmarks (e.g., BV, OD, OC, retinal nerve fiber layer(RNFL) or rim loss(RL)). These references contribute to 20/30 (70%) of papers, as shown in figure 6. Seventeen of them are blood vessels based methods; those references are[26,28,60,63–65,68–70,72,49,50,52,55–59]. Only two references[27] and[55] are optic discs based detection, and one reference[56] is RNFL based detection. See figure 7.

Another set of articles have used multiple landmarks, as denoted with black color in figure 5. They contribute to 10/30 (33.33%) of papers. Ref[54,67,71] have used BV and OD, while ref[48,51,53,61,66,] have used OD and OC to classify the disease. And ref[47] used rim loss (RL) and (RNFLD). Lastly, Ref[25] used BV, OD, and OC in their work.

The rest of the researchers used multiple landmarks, such as[48,51,53,61,66] have worked on OD and OC segmentation. References[71] and[54], worked on BV and OD segmentation, and only reference[47] has used RNFL and RL. The rest of the papers have used triple landmarks in their work, such as[28] and[67] who have worked on BV,OD, and background (BG), and[25] used BV, OD, and OC.

In the next layer of our taxonomy, articles are classified according to the discriminator's receptive field. As illustrated in figure 5, references with (P, H, or G) letters represent pixelGAN, PatchGAN, or ImageGAN, respectively. ImageGAN papers are ref[26,28,54,59,61,64,65,67,71]. While PixelGAN papers are[47,48,50–52,56,63,68,70]. And PatchGAN papers are ref[25,27,69,72,49,53,55,57,58,60,62,66].

Reference[24] proposed Pix2pix based conditional adversarial network(cGAN) as a general-purpose solution to image-to-image translation problems, and they demonstrated that 70x70 PatchGAN alleviates artifacts and achieves best scores. Scaling beyond 70x70 to full 286x286 ImageGAN, does not appear to improve the quality of the results, and in fact, gets a considerably lower FCN-score. This scaling mechanism may be because there are more parameters in ImageGAN than PatchGAN and greater depth, which made it harder to train. On the other hand, references[27,55,66] proved that 64×64 Patch-SAN is the best while[58] concluded that 120x120 patch is better than 64x64 patch size. On the other hand[54,65] concluded that ImageGAN is better than PatchGAN. Lastly, [69] Pixel level annotation is much more tedious than image level.

Each reference in figure 5 is denoted with a letter indicating the contribution of the relevant paper. Nearly 17/30 (56.66%) of papers have worked on segmentation task and denoted by (s), whereas 5/30 (16.66%) have worked on images synthesizing and denoted by (y), while only two papers have worked on classification task and denoted by (c). The rest of the papers 6/30 (20%) have worked on multiple tasks (e.g., sc,sy,ysc). Figure 8 shows the distribution of papers according to their task. Tables 2-8 in multimedia appendix 1 summarize literature results as reported in papers.

Reviews and Surveys category

In this category, two sets of reviews were identified. In the first set, detailed discussion about recent breakthroughs technique of GANs, its development, variations, and medical field applications. At the same time, the second set includes studies on the impact of deep learning on ophthalmology. Totally, this category includes twenty-nine out of 59 (49.15%) papers.

For the first set, refs[36–38,40–42,73–76] provided detailed reviews about GANs including their basic background, theory, and implementations. Also, present current research hotspots and proposed GANs in different applications. They provided the reader with a clear sight of GANs' advantages and disadvantages, its different evaluation metrics,_and proposed a bright prospect of this technique. Refs[73,36] focused on the importance of GANs, especially in medical field applications, and their capability of generating data through image synthesis technique without explicitly modeling the probability of density function. Ref[74] provided further investigation of GAN in parallel intelligence. Another study, ref[77] discussed incorporating GANs in the signal processing community, showing different training methods/constructing GANs and highlighting current challenges of their theories and applications. Ref[78,79] are practical prospective studies, where in[78], they tried to assess GANs algorithms and find the best architecture among all. However, they concluded that most of the models could achieve similar scores with enough hyper-parameters optimization and random restarts. Additionally, they tried to overcome the limitation of evaluation metrics by computing precision and recall on several proposed datasets. Also, in ref[79], authors reproduced the current state-of-the-art GANs aiming to explore their landscape, discussing their pitfalls and reproducibility issues. Ref[80] presented a comprehensive study about GANs by identifying the relationship among them to understand AEs and GANs better, emphasizing generative models' importance. Ref[81] proposed a starting point survey for those who have interests in deep generative models such as DBN, DBM, RBM, VAE and GAN. They explained their building blocks, learning procedures and limitations.

In the second set of articles, ref[31,33,46,82] presented an overview of DLs' applications in ophthalmic disorder using digital fundus images. They summarized the publicly available datasets used for different retinal diseases such as cataracts, retinopathy, glaucoma and age-related macular degeneration. They also provided a detailed summary of the pros and cons of this emerging technique for both computer scientists and ophthalmologists and specifying the clinical and technical aspects to address deep learning challenges and future directions. Ref[83–85] discussed the importance of clinical considerations and potential challenges for clinical adoption and telemedicine integration to reduce cost, increase accuracy, and facilitate healthcare accessibility. Ref[32] described the importance of deploying deep learning algorithms within clinical settings. Ref[34] clarifies the misunderstanding between machine learning and deep learning terms and presents an overview of artificial intelligent AI and its development in the ophthalmology field. Ref[86] also provided an overview of AI and deep learning DL applications in glaucoma detection using fundus images, optical coherence tomography, and visual field interpretation.

Other studies, [17] and [87] followed the systematic framework in their reviews. Where ref[17] discussed the main algorithms used for glaucoma detection using machine learning(ML), indicating the importance of this technology in the medical aspect, especially retinal image processing. While the latter, ref[87], conducted their systematic review on investigating and evaluating DL methods' performance for automatically detecting glaucoma using fundus images.

Figure 9 illustrates the publicly available dataset, their sizes, and how often researchers used them. Each dataset is collected using a particular camera with different standards and used for a specific disease type. Thus generalization is the key problem of DL approaches as described in the challenges section.

As figure 9 illustrates, DRIVE and STARE are the most frequently used datasets. In other words, researchers often rely on blood vessel segmentation in the diagnosing process[46]. However, few researchers have used Messidor-1, HRF, 2D Neurons(NeuB1), and CHASEDB. For OD and OC landmarks segmentation, DRIONS-DB, REFUGE, ORIGA, RIM-ONE (r3/v2), and Drishti-GS were used the most. And seldom used is the Large-scale Attention-based Glaucoma (LAG) dataset, which is for RNFL and RL landmarks segmentation.

Figure 10 shows the distribution of the collected papers per year regardless of their duplications. The statistics in figure 10 indicates the late interest of researchers to adopt GANs techniques in ophthalmology. Therefore, consideration should be taken into account for this defect, and intensive study should be conducted using this newly emerging technique.

This work has targeted five search engines: Scopus, Science Direct, Web of Science, IEEE, and PubMed, which are highly reputed and reliable resources for research. They provide studies about deep learning implementation using different retinal disorder fields to help ophthalmologists and patients. Figure 11 divides the current literature work according to their publication. Journals articles occupied thirty-six of papers and only twenty-three were published in conferences.

According to the report in multimedia appendix 1, each paper has used a different set of evaluation metrics; thus, we concord with[25] as concluded there are no uniform evaluation indexes in the literature to evaluate synthetic and real images. To further clarify this issue, figure 12 shows the distribution of evaluation metrics used in the collected papers.

Discussion

This study aims to provide a detailed summary of literature works on retinal disease detection or segmentation, particularly glaucoma, using GANs, and highlighting recent trends of researchers in this topic. We mainly focused on the articles that worked on enhancing the segmentation or detection process of the disease rather than improving GANs techniques. Furthermore, we provided a taxonomy of papers related to this area for further assisting future research.

Several benefits may arise from our taxonomy. Firstly, organizing tens of papers in a single diagram, interested people in this area might be confused by many papers without the existence of organized structure. As a result, fail to get a proper understanding of the actual activities in this field. Secondly, it helps sort literature works and activities into meaningful, easy to manage, and coherent frameworks. Thirdly, it provides researchers with better insights on a given theme, thus finding current literature gaps and discovering new research directions. Lastly and most importantly, it may help highlight articles' strengths and weaknesses of the research scope.

From the developed taxonomy, we can quickly notice that all the published papers have followed the direct method of GAN's architecture; hence there is a great need to discover the impact of the hierarchical or iterative method in glaucoma screening. Moreover, almost all of the researchers have worked on blood vessel segmentation, and very few have used the optic disc and optic cup segmentation, which are the most reliable indication of glaucoma by ophthalmologists. Future GAN's research should focus on the disease classification rather than the segmentation of retinal anatomy. Most of the literature work faced difficulties in early detection of glaucoma and low segmentation of fine vessels; therefore, alternatives should be taken place, e.g., using RNFL to indicate an early presence of the disease or exploiting prior knowledge of vascular connectivity to improve segmentation performance better. Although RNFL is a good sign of early screening of glaucoma, very seldom studies utilize RNFL with GAN. Optic disc/optic cup segmentation may lead to interference with pathological aspects such as genetic large OD sizes. Based on the reviewed papers, we noticed only one single work used RNFL for glaucoma screening. Although they achieved impressive results, however, they used a private dataset.

Most of the previous studies concentrated on the segmentation task. Nearly 17/30 papers worked on retinal landmarks segmentation, while only two papers have worked on disease classification, and five papers worked on images synthesizing to tackle the lack of medical images. However, the rest of the papers (6/30) performed multiple tasks (e.g., segmentation and classification, synthesizing and segmentation, etc). Therefore, researchers should increase their efforts to cover this gap in future studies.

In the following sections, the included papers will be discussed in detail. We presented comprehensive diagrams showing the factors that motivate researchers to carry out their work in this area, highlighting their encountered challenges and summarizing significant recommendations to address their faults in future work.

Challenges

Glaucoma is a serious disease. Therefore, researchers and developers attempt to exploit the magic of DL technique to help doctors and patients diagnose the disease at its early stage. However, various challenges hinder their expectations; some of those challenges implicitly exist in the nature of DLMs, or somehow incorporated with it (e.g., data richness, diversity of data, and powerful hardware), beside the challenges of GANs architectures (e.g., model collapse, optimization, Nash equilibrium, and evaluation metrics). All these challenges have been summarized and discussed in this section along with their relevant references to provide the reader with direct access to the original papers for further discussion. Figure 13 categorizes literature challenges into six groups to further assist discussion. Each group is indicated with a separated shape.

Challenges related to patients

The silent progress of glaucoma disease constitutes a crucial challenge worldwide. Half of the infected people do not experience any symptoms at early stages[5–7]. Studies reported more than 60 million cases diagnosed in 2013 globally, and it is expected to exceed 75 million and 111 million cases by 2020 and 2040 respectively[9,10]. According to[85], glaucoma is not cost-effective in developed countries, however, it is in India[88] and China[89] and other developing countries, especially in rural populations. These populations suffer from difficulties to access medical centers, experts unavailability, cost affordability, and sustainability of healthcare services[90]. In addition to the curse of a pandemic, Covid-19 recently hit the globe, which enforces social distance during communication. Therefore there is a great need to promote the work of ocular screening to work in conjunction with telemedicine as a remote monitoring tool[91], alongside with presence of handy cheap smartphones, whereby patients can collect their own IOP data themselves with accurate tonometers and free anaesthesia[92]. Although DLMs positively affect both doctors and patients' style in terms of decision-making, cost affordability and healthcare accessibility, there are still serious challenges such as technical and clinical challenges, interpretation of the results, patient trust in machines[91]. Reference[93] expect that shortly, artificial intelligence will assist specialists in achieving high levels of consistency and accuracy beyond human abilities

Challenges related to reliability

Reliability is the key to adopt computer technology in the medical field. Deep learning techniques may misclassify segmenting some pixels due to low image contrast or heavy overlap between foreground and background pixels, leading to false-positive/negative result[27,55]. In some cases, doctors are dissatisfied with deep learning segmentation performance as it is not as real as their expectations. Taking an example of RNFL segmentation, the segmentation results do not have specific geometrical shape of RNFLD as the gold standards and large segmentation errors of fundus images[57]. Furthermore, the variability of shape and extremely inhomogeneous optic disc structure appearance result in inaccurate CDR measurement compared with ideal ones[94–96]. In some cases, deep learning approaches neglect domain knowledge that doctors care about, like CDR[97].

Often existing methods suffer from low segmentation of the fine vessels[54,52], due to weak ability of anti-noise interference or insufficient segmentation of vessels[63], prior knowledge of blood vessels connectivity may improve the segmentation performance. Meanwhile, the low reliability of manual detection and the small size of public datasets increases the complexity of morphological assessment of non-glaucomatous optic neuropathy[98,99]. Robust ground truth labeling must be generated after a comprehensive evaluation, including structural imaging, clinical examination, and perimetry[100]. Doctors mostly decide the disease status. Even though all clinical symptoms occur, it can lead to differences within annotators, hence exaggerated annotations[31,85,101,102]. The reliability of glaucoma algorithms is restricted due to the lack of reference ground reality for glaucoma[103,94]. DLMs have a remarkable ability to address glaucoma. However, it is critical to have gold-standard algorithms for assessing and detecting glaucoma[33], as well as for editing or synthesizing images using GANs techniques[75].

Sometimes, researchers tend to exclude low quality or sparsely annotated images during the training phase; this kind of regime weakens the algorithm and leads to less reliability in real-life cases[90]. Furthermore, incorporating non-specialists for image grading limits the reliability of identification[104]. Finally, although most of the reviewed papers have shown outstanding diagnostic performance, some did not mention the consideration taken while calculating the independent datasets performed[91]. Excessive screening can result in overdiagnosis. DLMs could also be harmful if the diagnostic software were issued directly to patients as future opportunities and risk of artificial intelligence could be magnified[34].

Challenges related to biological effects

Pathological change and image quality play a major role in the accuracy of glaucoma diagnosis[27,47,102]. Early and moderate glaucoma stages are considered one of the biggest challenges faced by ophthalmological practice; due to the marginal variation size of CDR compared to normal eye[105]. Reference[106] has used ResNet-50 and GoogLeNet with transfer learning for early and advanced glaucoma detection, and they found that GoogLeNet outperforms ResNet-50 with a trade-off performance between Se and Sp. Also, [55] proposed GAN–based optic disc segmentation method allied with an index of taxonomic diversity for extracting texture attributes aiming to detect early stages of glaucoma. They achieved outstanding results reaching up to 100% for accuracy and 1 for the ROC curve. The misclassification of glaucoma and non-glaucoma is usually due to heavy overlap and extremely bad contrast between ocular structure and the background, leading to unsatisfied segmentation performance due to OC's undistinguishable boundaries[95]. Low-quality images (blurring and contrast) can cause model predictions unreliable. Also, the lack of a clear OC border increases the misclassification rate[107].

There is a tradeoff between image's quality and computational parameters of the network[108]. Therefore, the need for DLMs to downsample images into lower resolution (i.e., 224×224) to reduce the computation time leads to reducing image contrast, hence deteriorating key diagnostic parts of ocular and weaken the capability to recover contextual information[61]. On the other hand, DLMs performance varied among ethnicities, e.g., the Saudi population's performance is not the same as on western populations. This significant difference is due to the richness of melanocytes in the retinal pigmented epithelium (RPE) of darkly skinned people compared to white people[31]. Therefore datasets used in glaucoma detection must follow specific standards to ensure heterogeneity and diversity of images.

Multiple eye disorders such as high myopia or pathologic is another major challenge that leads to false-negative results[33]. Megalopapilae and myopia cases mostly cause misclassification of glaucoma due to their irregular ONH appearance[109]. In other cases, it is hard to distinguish between physiologic large cups and glaucomatous cases because both cases share a common feature (e.g., large CDR)[96]. Diseases such as optic disc edema, optic disc hemorrhage, and glaucoma frequently make segmentation of OD rather difficult[110]. On the other hand, retinal blood vessel segmentation also has inherent challenges such as incorrect segmentation of pathological details and low microvascular segmentation[111].

Challenges related to availability/services

Time, efforts and lack of experts are the main challenges of medical care centers[65,112]. Therefore computers have been increasingly used for automatic retinal segmentation to serve as a second opinion to the doctors, improve the diagnostic accuracy and reduce the tedious work of annotating images[25,72,113]. Particularly, GANs showed impressive performance in medical image synthesis and it is usually employed to tackle the shortage of annotated data or lack of experts[48,53,73]. Generally, medical images are usually rare, expensive and full of patient privacy issues[59,65], the publicly available datasets are often imbalanced in size and annotation[25,27,58]. In general, segmentation tasks suffer from an immense problem of class imbalance. Thus the accuracy metric is not sufficient alone until concluding a system's efficiency, on both sensitivity and specificity. They should be considered as an essential evaluation metric[46].

Reference[67] proposed a GAN method with semi-supervised learning to develop a good image synthesizer to tackle the shortage of retinal image availability and support generalization ability. Additionally, reference[114] created a large-scale database of glaucoma diagnostic fundus images (FIGD) database. It proposed the Glaucoma Diagnosis With Complicated Neural Networks (GD-CNN) method for automatic detection of glaucomatous optic neuropathy(GON) with the potential to be generalized throughout populations.

Various GANs-based methods have been proposed to mitigate image labeling[49, 59,62,69,70] and [72]. However, this challenge remained open as the current literature results are still inaccurate (e.g., fail to generate very thin vessels). The latter[72] concluded that the diversity of annotated images is more important than the actual number of annotations. Finally, rural areas experience difficulties in locating ophthalmologists. This also necessitates more future work to use telemedicine in ophthalmology[34].

Challenges related to the nature of deep learning

With the recent advancements of DLMs, promising results in the field of ophthalmology have been obtained. Many GANs and CNNs models are proposed in computer vision. However, DL approaches face several difficulties, such as domain shift.

Domain shift is the disparity in appearance distribution between various datasets due to various camera settings, illumination variation, different screening angles, or the region of interest might be out of focus. As a result, domain shift hinders the generalization capability of deep networks[66]. In most literature, training and test of data come from the same image distribution. However, this is not always the case in real life. Therefore it may significantly damage the real-life applications if it is not handled beforehand[46]. Reference[53] proposed an unsupervised domain adaptation framework by learning domain invariant features to enhance segmentation performance and generalization capability. Another paper[51] tried to align the distributions of the source and target domains so that the labeled source images can be used to enhance the classification efficiency of the target domain.

Deep learning addressed many issues in the traditional methods of machine learning. However, it also brought new difficulties. The most crucial issue is the ambiguity of the diagnosing result; in other words, the black-box problem[32,83]. DLMs are black-box in nature and do not have diagnostic explanations to confirm their effectiveness in a real clinical setting. Reference[47] proposed a pathology-aware visualization approach for feature visualization using DNNs to explain better how decisions are taken by computer and, therefore, find pathological evidence through computer-aided diagnosis. Furthermore, reference[94] proposed a weakly supervised approach because of its high potential to learn the evidence and optical disc from large-scale weak-label data, thus further improving the trust diagnosis of glaucoma.

The lack of publicly available datasets for training the model is another significant challenge of deep learning approaches. Therefore, reference[109] proposed a dataset named Retinal Fundus Glaucoma Challenge(REFUGE) dataset, which contains 1200 fundus photographs with standard gold segmentations and clinical glaucoma marks. Moreover, reference[115] created large-scale-attention-based glaucoma(LAG) database containing 11,760 fundus photographs classified as either positive glaucoma (4,878) or negative glaucoma (6,882), the largest existing ones so far. According to[31], the key problem of constructing a robust deep CNN method is not the availability of broad datasets but the diversity of annotation of those images[72]. A major difficulty of each algorithm is its validity in multiple patient cohorts with diverse conditions. Therefore, to get a sturdy DLM, it must be effective across various datasets[84].

Recent studies demonstrated more complicated and informative image features might be discovered when growing the depth of the network[116,117]. However, as the network depth rises, deeper CNN also has poor diagnostic efficiency due to the gradient disappearance issue or the gradient explosion problem[65,118,119]. Researchers mostly use shortcut links (skip connections) that skip one or more layers while training deep networks such as[65,105,107] and[108]. Alternatively, in GANs techniques, using Wasserstein GAN or Least Squares GAN (LSGAN) gives a smoother gradient that contributes to stable training[53,26]. Another concern that should be considered before building up deep neural models is, the computation time. As there is a tradeoff between the model's depth and the efficiency, the number of parameters is significantly linked to the network's depth[118].

Challenges related to GANs techniques

With all the developments and studies ongoing, GANs suffer from several challenges and weaknesses besides the challenges related to deep learning nature (e.g. black-box, generalization capability, computation time and annotation cost etc.). The most critical concern in GANs is the instability of the training process (Nash Equilibrium point)[76,120]. Reference[56] used the residual module to efficiently help competitive networks easy to optimize, however,[52] used Wasserstein GAN Gradient Penalty (WGAN-GP) in their work to alleviate training instability of the traditional GAN. Another paper [70] carefully adjusts hyperparameters to balance between the two networks (G&D). Reference[64] improved learning performance and mitigated imbalanced learning by introducing new loss functions for the Generator and redesigning the discriminator's network. However, it is still challenging to determine which algorithm works better than others or what modifications are critical to enhancing the results. Reference[78] found that most models could achieve comparable scores with appropriate hyperparameter optimization and random restarts. According to[79], the non-saturating loss over datasets, architectures, and hyperparameters is sufficiently stable.

Also, in GANs, the possibility of mode failure/collapse persists during model’s training. Model collapse occurs when data generated from GANs mostly concentrated on very narrower modes (partial collapse), or one single-mode(complete collapse)[40,77]. On the other hand, if the discriminator becomes very strong during training, the generator gradient gradually decreases and eventually disappears. As a result, the generator learns nothing. The imbalance between generator and discriminator networks contributes to overfitting. Many approaches have been proposed to tackle these challenges, like reference[43] aimed to address instability training issues, and[53] created a new adversarial domain adaptation architecture, led by Wasserstein for better stability and convergence.

The lack of standard evaluation metrics is another big issue in GANs compared to other generative models. Inception Score (IS), Average Log Likelihood, Frechet Inception Distance (FID), Wasserstein metric, etc. are GANs quantitative measurements. There is no majority vote on which assessing measurement is the best. Various scores rely on various aspects of the way of generating images. But some measurements seem more plausible than others, such as FID is more durable to noise. FID can compare the similarity between real and generated images[121], which is considered more effective than IS[42].

In conclusion, the main causes of GANs problems can be summarized in two points. 1)The distance calculation of the corresponding optimization (such as Kullback-Leibler (KL) divergence and Jensen-Shannon (JS) divergence) is unreasonable. 2)It is difficult to overlap the generated distribution with real distribution. Although GANs technique is a new interesting and attractive field of study in many applications, further studies are needed to solve the uniqueness of generated samples, poor convergence, and complete model collapse challenges.

Motivations

Adopting deep GAN in ophthalmology is a promising and significant field of study. This section reports some of the literature's characteristics, which we classified on the basis of references to support further discussion, as figure 14 shows.

Motivates related to experts/doctors

Detection of any retinal defects must be through analysis of ocular images. Analysis of retinal images, though, must involve trained physicians to analyze and assess digital color fundus images. Such a process requires a great deal of time and human work; therefore, GANs support doctors in mitigating this extensive work bottleneck[59,68,69]. Furthermore, Deep GANs techniques are unlike CNNs, where the same GANs approach could be applied on a wide variety of cases and still produce reasonable results[24]. GANs can detect the OD in fundus photos with pathological changes or irregular highlights[27,61]. In the case of vessel segmentation with CNN-based methods, outputs are usually blurry around small and weak branches or suffer from a problem of non-connectivity of segmented vessels; however, GANs better segment capillary/thin vessels of fundus images[50,54,58] , thus serve as a second opinion to ophthalmologists[46]. GANs are the framework that allows to create and use of practical outputs as a gold standard[23]. Therefore, these frameworks were adopted by[57] due to their ability to generate the required specific geometry of RNFLD, which is close to ground truth with high precisions, accuracy, and fewer segmentation errors, even though the existence of multiple pieces of RNFL or low images contrast, hence its segmentation results are much more trusted by doctors than CNN's.

Adversarial learning avoids scarcity of manual annotation and subjective segmentation made by non-expert clinicians as this methodology is mainly data-driven[46,60]. In glaucoma classification, enforcing GAN to synthesize images with similar visualization results as the reference image will help mitigate the drawbacks of binary labels(negative or positive) that limit the visualization methods to recognize pathological facts hidden behind the reason of DNNs diagnosis[47].

Motivates related to researchers

Deep learning in retina images is very effective and useful[46]. However, they are often affected by domain shifts across datasets. As a result, a generalization of DLMs was severely hindered. Therefore, researchers tend to exploit generative adversarial learning for domain adaptation by encouraging the target domain predictions to be close to the source ones[53,66]. Domain adaptation is often used to overcome the lack of large pixel annotation using off-the-shelf annotated images from other relevant domains. Alternatively, researchers exploit the existence of a large amount of unlabeled data to train a classifier using the power of DCGAN in a semi-supervised learning[67]. Semi-supervised learning is in a middle way between unsupervised and supervised learning; therefore, less human intervention is required when combined with GANs for better semantic segmentation[48]. Using GANs techniques, reference[72] performed image segmentation with very few annotated samples (0.8-1.6%), nearly 500 to 1000 annotations. Also,[71] proposed image synthesizer using GANs with style transfer then integrated the outputs into the training stage to boost segmentation efficiency using ten samples only.

With deep adversarial learning, researchers aim to reduce domain discrepancy[122,123], by improving the quality of the generated outputs to be as close as possible as the inputs. Reference[51] exploit label information for matching domain distribution. Another paper applied the least-squares loss function instead of sigmoid cross-entropy to generate images with distribution close to the real ones and alleviating gradient vanishing problems as well[26]. Also, Reference[27] added a patch-level adversarial network to enhance image consistency between ground truth and the generated samples, which further boosts segmentation performance.

GANs networks are capable of learning the mapping from the input image to output image as well as learn a loss function to train this mapping[24], unlike existing DLMs, which use a unified loss function for retinal vessels segmentation, therefore produces blurry outputs with false positives(fp) around faint and tiny vessel[58]. In contrast to GANs variations (e.g., WGAN-GP and M-GAN), which provide accurate segmentation results around small and weak branches[52], reduce low micro-vascular segmentation[64] and preserve the connectivity of arteriovenous vessels[50]. Moreover, autoencoders and GANs in a single system facilitate generating vessel maps without the previous existence of retinal vessel tree[62]. Also, unconditional GANs(uGANs) can synthesize retinal images needless to use prior vessel images[70].

The existing DCNN method lacks sufficient feature extraction, weak generalization capability, and poor capability to recover low context information, unlike GAN, which is used to alleviate these problems as in[61], which proposed GAN with transfer learning, data augmentation, and skip connection concepts to overcome these challenges. Other researchers[55] impressively improved glaucoma segmentation and classification results using GANs allied with texture attributes identified by taxonomic diversity indexes. They achieved promising results, reaching up to 100% for SE, SP and Acc.

For optimizing network complexity, reference[63] applied the attention Gates technique in a standard GAN to encourage the propagation of features, promote reuse of features and greatly reduce network parameters when paired with Densnet instead of conversion layer. Alternatively, using dilated convolutions in the generative networks effectively expands the generator's receptive field without the number of calculations[56]. Adversarial training has been shown to improve the long-range spatial label interaction without expanding the segmentation network's complexity[124].

Motivates related to medical centers

We think the best medical treatment is achieved while the doctor-patient relationship is built on honesty and concern. DL cannot substitute real relationships-but can complement them[82]. GAN architectures are versatile. For various training samples, the objective feature can be redesigned, and more free model design[76]. The extraordinary feature of GANs in the medical field is synthesizing high-quality images with global consistency(e.g., color consistency and both BV and OD occupy the same proportion area as the real images)[28,70]. Reference[55] proposed a method that learns the mapping function between retinal landmarks (BV, OD and OC) and synthesizes images using the three channels RGB. Furthermore, it exploits the merit of a large receptive field of GANs to generate good segmentation results[56].

Incorporating GAN techniques in the medical field helps enrich healthcare centers with various data and effectively solves data imbalance problem[62,112]. As a result, this feature facilitates solving ethical issues regarding patients' privacy[46], saves memory and time needed to images collecting[53], reduce costs[65], and saturates the nature of data-hungry of DLMs[59].

Recommendation

In this section, we briefly included literature's guidelines to alleviate existing challenges faced by researchers, doctors, medical centers, and patients, besides simplifying ways to achieve a correct diagnosis of retinal defects. See figure 15.

Recommendations to doctors and medical centers

Image resolutions significantly improve GANs performance[62,125]. The key factor of getting GAN's high-quality synthetic outputs is the high resolution paired images and the architecture of the generator[25]. Moreover, annotation variety is more important than the actual amount of annotations[72]. Therefore, doctors must develop a public dataset with high-resolution images that meet the quality assessment system[84]. Furthermore, it must be accessible and multi-ethnicities to ensure generalization capability[87], experts must validate deep learning models on the sizable heterogeneous population under different conditions[31]. Otherwise, direct release of DL application could be harmful without beforehand checking[34]

To improve public health, reduce healthcare costs, and enhance patients' perception, doctors shall adopt DL techniques in the medical field to tackle these challenges[32]. Adopting deep learning applications in MRI and X-ray image processing is also interesting[71]. All glaucoma researches emphasized the importance of CAD programs for early disease detection and improved the reliability of the screening[17].

Future GANs techniques may have the ability to understand humans and further explore world[38]. Innovative and radical solutions for the healthcare system must be improved along-side glaucoma screening[85]. Significant improvements in instrumentation and interpretation can lower the cost of glaucoma screening in the future. Embedding glaucoma AI algorithms in the electronic medical record to improve outpatient management[86], It would be up to the physicians to lead the way in deciding how to incorporate AI for a new era of glaucoma management.

Automated retinal imaging technologies can reduce barriers to access and monitoring of the health system. Thus, AI integration into ophthalmology can improve patient care[83], help clinicians focus on patient relationships, and enhance health-services[82] that decrease irreversible blindness[33]. GANs can reduce the scarcity of manual data annotation and can also be used as a clinical support tool[46].

Recommendations to developers

A CNN in a generative learner is used for image segmentation tasks and obtained successful outcomes[126]. GAN is an inclusive system that can be combined with various deep learning models to address problems that conventional machine learning algorithms cannot solve e.g., such as poor quality of outputs, insufficient training samples, and deep feature extraction[40]. Furthermore, it outperforms conventional methods in editing and synthesizing image[41]. GAN allied with transfer learning can effectively reduce misjudgment of OD/OC in glaucoma cases and improved accuracy and generalization capability; however, better backbone network and different upsampling methods are required to improve performance[61] and exploring other downstream tasks may enhance the model's performance[71]. Although the vast increase of GAN applications, further studies are required to improve its efficiency and performance[42]. Incorporating spatial information, attention-based information, feature-maps information, and image channels(RGB) to improve network performance is a current research trends[118].

GANs can generate samples with distribution close to real data. Thus it can be used in a systematic study of parallel systems[74]. GANs or their variants are the future trends for mitigating imbalanced learning through generating samples close to real data, or enhancing model performance when combined with variational auto-encoders(VAEs)[28,37,46]. Thus, it is used as a sophisticated data augmentation technique to generate heterogeneous samples and ensure prognostic characteristics of images[31].

To date, only a few studies have experienced AI technologies in teleophthalmology[83]; shortly, smartphones' photography can be used as a diagnostic tool for ocular diseases[84]. Nowadays, there is a great need for remote disease monitoring and screening[86], especially during today's Covid19 pandemic. Therefore, deep learning and telemedicine/teleretinal are potential game-changers in the eye-care field[85].

Reference[66] proposed a very lightweight network architecture for joint optic disc and cup segmentation based on MobileNetV2 backbone, which has few parameters and half testing time compared to Xception backbone, which promotes their network as a mobile application for glaucoma detection. Another research[55] presented GAN and texture features for automatic detection of glaucoma, and they achieved impressive results that reached up to 100% for Se,Sp, and Acc, and they proposed to transfer their method into mobile application in future studies.

Future research should emphasize GANs and semi-supervised learning for image synthesizing, aiming to improve the classification accuracy and the quality of the generated images[49,67,72] simultaneously. Adopting GANs in the medical field is still in its infancy, with no breakthrough application yet clinically implemented for GANs-based approaches[73]. For better feature extraction, researchers must exploit full feature information of RBG channels, spatial structure, and geometry of landmarks[57]. Semantic segmentation may reduce manual labeling effort[48,69] and enhance model performance when incorporated with WGAN domain adaptation[53]. In ophthalmology diagnosis, adversarial domain adaptation can be an important and effective direction for future research[46,65,127]**.** Also, exploring the relationship between the quality of the generated image and the performance of the CAD system is needed[25].

With the envision to improve deep learning performance, pre-processing and post-processing are essential for accurate segmentation[31,54,64,]. Reference[17] concluded that dataset size has a huge impact on the results. However, reference[72] amazingly demonstrated that annotation diversity is more important than annotations count. GAN can make use of large amounts of unlabelled data[38,62].

Regarding GANs evaluation metrics, future studies should focus on more objective and systematic evaluation methods. Further FID examination is required[78]. Developing quantitative assessment metrics is a crucial research direction[128,129]. Researchers should evaluate their segmentation performance on public datasets[48] with heterogeneous and multimodal using less data-hungry algorithm[84] Additional to examining other classifiers performance, e.g., XGBoost and other cGAN architectures for faster and more accurate learning[55].

For glaucoma diagnosis, CDR and ISNT metrics are substantial information to be assessed[17]. More studies are needed to assess the validity of ophthalmology applications to detect AMD, diabetic retinopathy and glaucoma in terms of Acc, Se and Sp[33]. AUC, sensitivity, and specificity should be stated in AI studies as the bare minimum[32].

Moreover, future research may utilize fine-tuning and data augmentation techniques to effectively improve model performance[31,55,61] and increase dataset size for better training hence better classifier[51]. GANs strength lies in its discriminator[36,54]. Duplicating the generator's structure improves robustness[64]. Adding more networks' layers help to capture more in-depth features[56]. Training and optimizing of the model are critical[58,62] , concerning careful balancing between G&D[70]. Utilize images patch-based as input for both G&D[58,59]. Use U-GAN instead of U-Net to improve the model's performance[63]. Additionally, exploiting previous knowledge of vessel structure[52,54,70] is critical for accurate segmentation[68]. Objective function supported with various loss functions may enhance model performance[58], for example, WGAN-GP can avoid gradient disappearing and enhance training[70], Dice coefficient loss function for segmenting hard images[27], and least-squares loss function with dilated convolution can enhance small vessel segmentation[26]. On top of that, topological structure loss can enhance the connectivity of A/V classification[50,] whereas binary cross-entropy loss function with false-negative loss function can improve training efficiency and increases segmentation robustness[64]. Furthermore, an adversarial loss can reduce the domain overfitting[130], and Wasserstein distance is preferable for domains adaptation as it decreases the probability of mode collapse and avoids the gradient vanishing[53]. Weight Normalization, along with Average Pooling is the best design setting when structured prediction is used with U-Net[72]. Explore a combination of different styles together instead of training dedicated models for particular styles[71]. MISH is a modern activation function that showed better results than ReLU on the most current benchmark datasets[131].

To date, explainable DLMs for glaucoma screening utilizing retinal fundus images have not been proposed[132]. Researchers should focus on relational and locational explanation using saliency maps, heat-maps, or other invented methods, to provide plausible explanations of DL decisions.

Lastly, future research incorporates the distributed ML library GPipe proposed by Google[133] to mitigate hardware limitations. This may help training large size models and enhance performance without tuning hyper-parameters[118].

Recommendations to Patients

Increasing the amount of data using a successful GANs synthesizer significantly saves a patient's privacy[46]**.** Good DLM offers timely treatment by providing wealthy information regarding patient's eye conditions[63]. Soon, AI supports telemedicine platforms by facilitating the self-monitoring of the patient through home-based diagnosis[83]. The existence of cheap handy smart-phones may also assist as a remote diagnostic tool[84]. As a result, increasing patient's perception and satisfactions[32], furthermore, motivates patients for continuous follow-up and treatment[85].

New direction of DL

Recently, DLMs have obtained positive retinal disease identification and segmentation outcomes. These technologies can revolutionize our way of life, and probably in the next few decades, the field of medicine changes rapidly[32]. However, these techniques are expensive hardware(e.g. GPU requirements) and greedy for images in their nature. Thus more advanced data augmentation techniques must be introduced, which create heterogeneous samples while preserving the prognostic features of fundus images, and a possible approach is to explore the generative adversarial networks (GANs)[31,134]. Building systematic deep learning models trained on heterogeneous and multimodal data with less data-hungry algorithms can boost artificial intelligence in clinical settings[84]. Additionally, Incorporating AI algorithms into the electronic medical record to promote outpatient management in another fascinating subject[86]

From the viewpoint of accessibility, cost-effectiveness, and healthcare protection, there is a tremendous need to promote remote glaucoma monitoring for developed countries and rural communities, allowing glaucoma patients to obtain their own IOP data with anesthesia-free and reliable tonometers[92], as well as home-based evaluation and disease control(e.g. rendering home-tonometry accessible at lower cost). Most importantly, within the current situation of Covid-19 pandemic, new directions of DLMs can be implemented via tele-retinal screening apps in ophthalmic settings to maintain maximum protection for both physician and patient at a lower expense.

Improving the quality of diagnosis in terms of class imbalance, refining the training phase of GANs, and enhancing the computation time to better diagnose glaucoma variants are obstacles for potential study[17,31,78]. Furthermore, it is necessary to note that GANs have not been used to diagnose difficult retinal disease up-to-date, and GAN evaluation metrics are still another challenging path of study[40].

Lastly, combining GANs with other approaches is another prospective potential research e.g., fusing GANs with reinforcement learning, function learning, or conventional learning to create new AI applications and facilitate the advancement of these methods is also worth investigating[38,76].

Limitations of study

This work's most important limitation is the number and identification of the source databases, but it is a reasonable and broad representative selection of the chosen sources. Furthermore, excluding other retinal diseases but glaucoma, due to its severity worldwide, is considered another limitation of this study. Besides, the fact that a quick view of the research activities on this critical trend of retinal disease and GANs does not necessarily reflect the research community's response.

Conclusion

Preserving adequate health services to people with retinal disorder has been a global issue. The study is still underway to diagnose retinal disorders using deep learning, however papers adopting GANs in glaucoma are not as abundant as DL or ML methods. Consequently, insights into this emerging area are needed. Nearly, less than five papers worked on glaucoma classification based GANs and the majority tend to use GANs for segmentation or synthesizing retinal images.

The contribution of this study lies in analyzing and taxonomizing literature works in glaucoma detection using GANs methods. To the best of our knowledge, all the previous work generally discussed AL or DL effects on retinal diseases, and none has particularly surveyed GAN in glaucoma. This makes our work first in this emerging technique.

According to our taxonomy, the majority of the collected papers paid more attention to single landmark segmentation (e.g., blood vessels). Some techniques were of tremendous or less interest (e.g., DCGAN and conditional GANs). Researchers worked in this field, identified their difficulties, and suggested recommendations to overcome the current and expected challenges. Other studies focused on improving GANs architectures than adopting them for diagnosing issues. To date, there is no specific work adopting GANs as a smartphone's application, nor in telemedicine. Therefore, filling this gap is important for both patients and physicians to ensure less physical meeting during the global Covid19 pandemic. Furthermore, new directions in this field have been explained.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Abbreviations

GANs : Generative adversarial networks
DCGAN : Deep convolutional generative adversarial networks
cGANs : Conditional generative adversarial networks
DLMs : Deep learning methods
DNNs : Deep neural networks
CNN : Convolutional neural network
BV : Blood vessels
OD : Optic disc
OC : Optic cup
CDR : Cup to disc ratio rule
ISNT : Inferior, Superior, Nasal and temporal rule
ONH : Optic Nerve head

RNFL : Retinal nerve fiber layer
RL : Rim loss
RGB: Red green blue
ROI : Region of interest

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Supplementary Files

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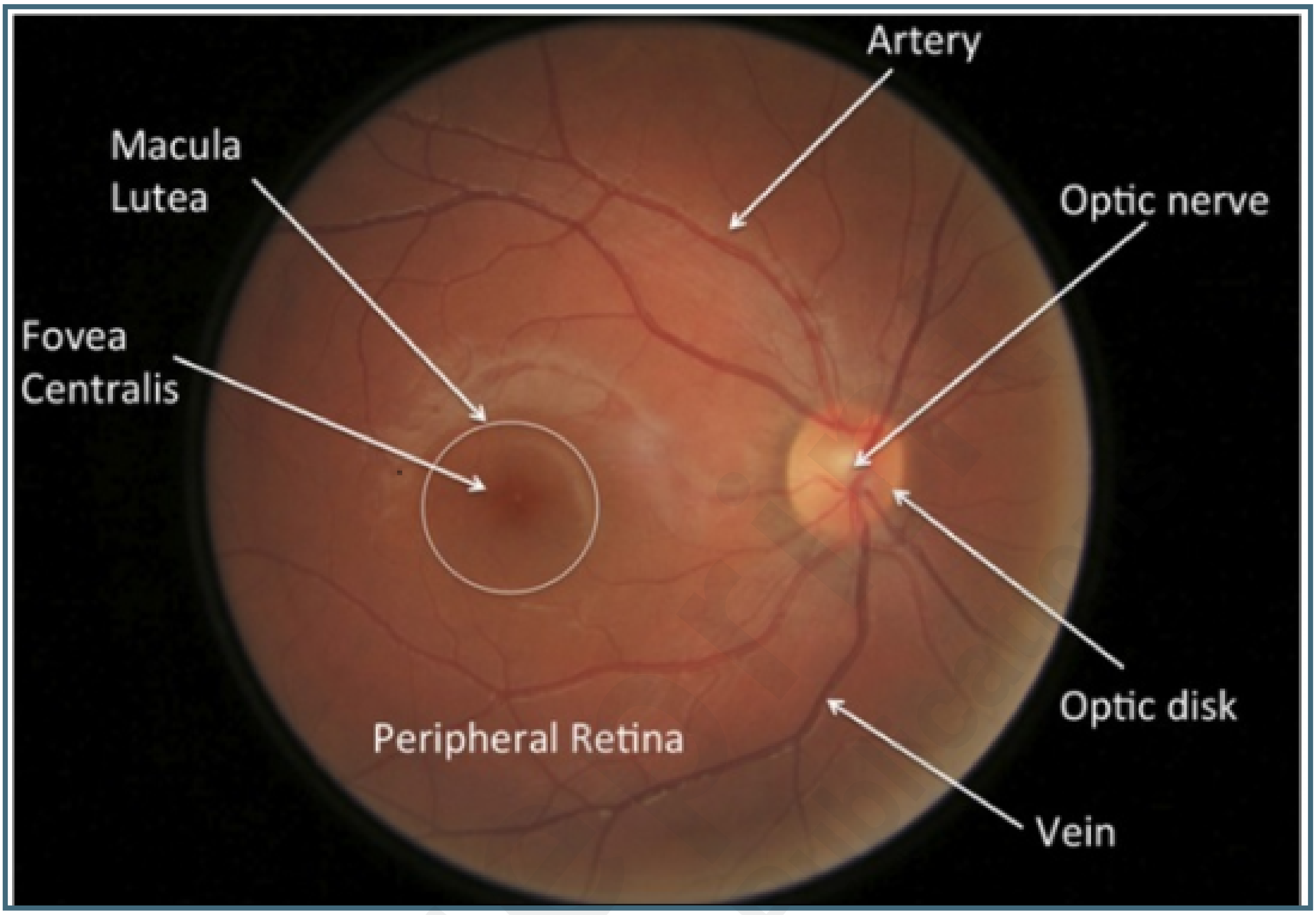
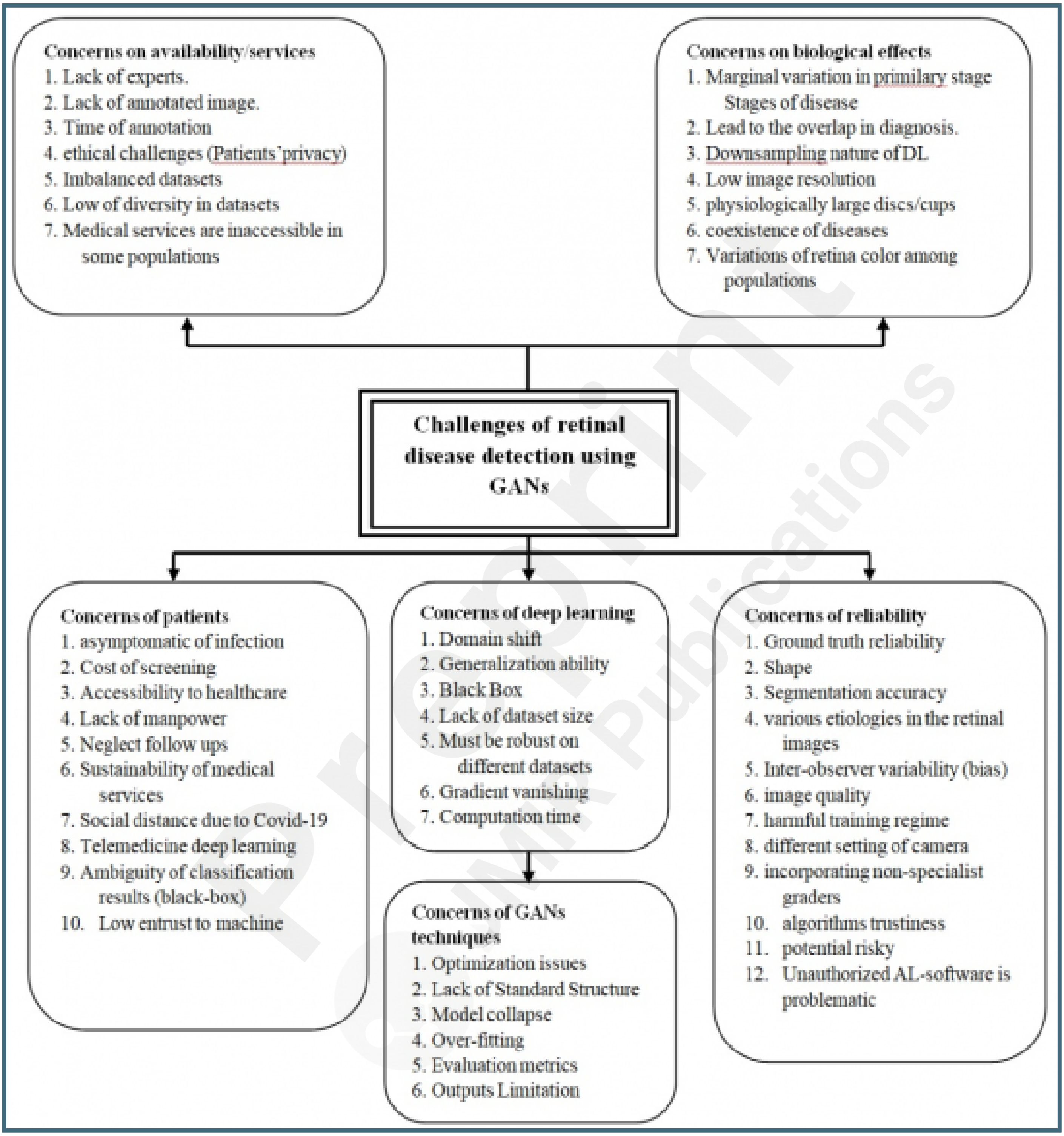
Figures

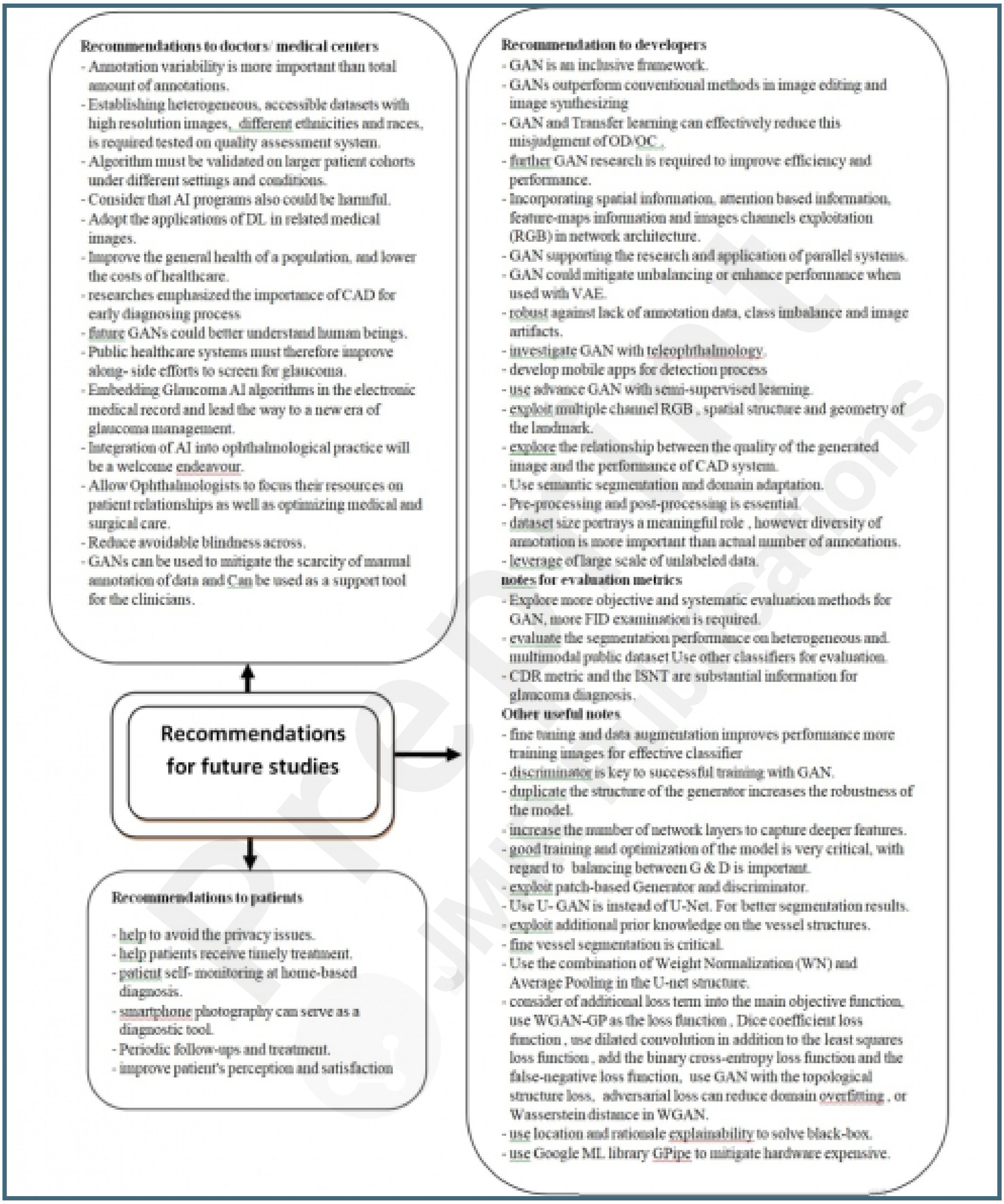
Fundus image structure.



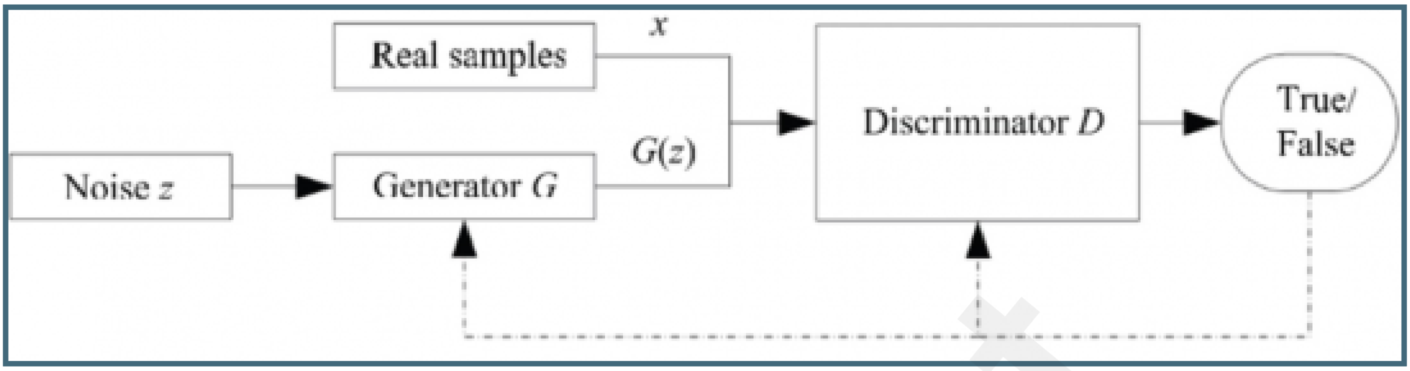
Challenges categories for glaucoma screening based on GANs technique.



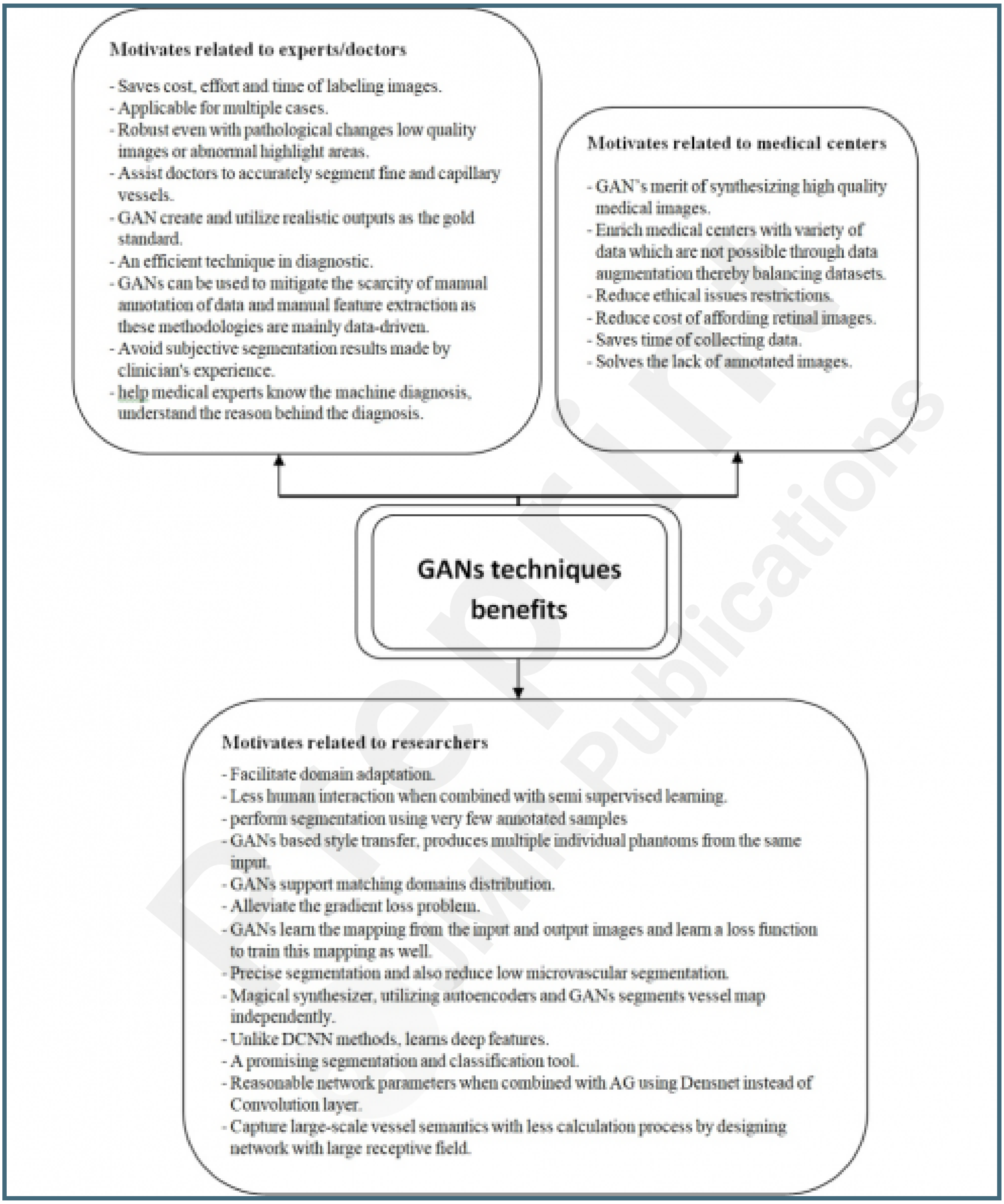
Recommendations categories for GANs-based methods on glaucoma screening.



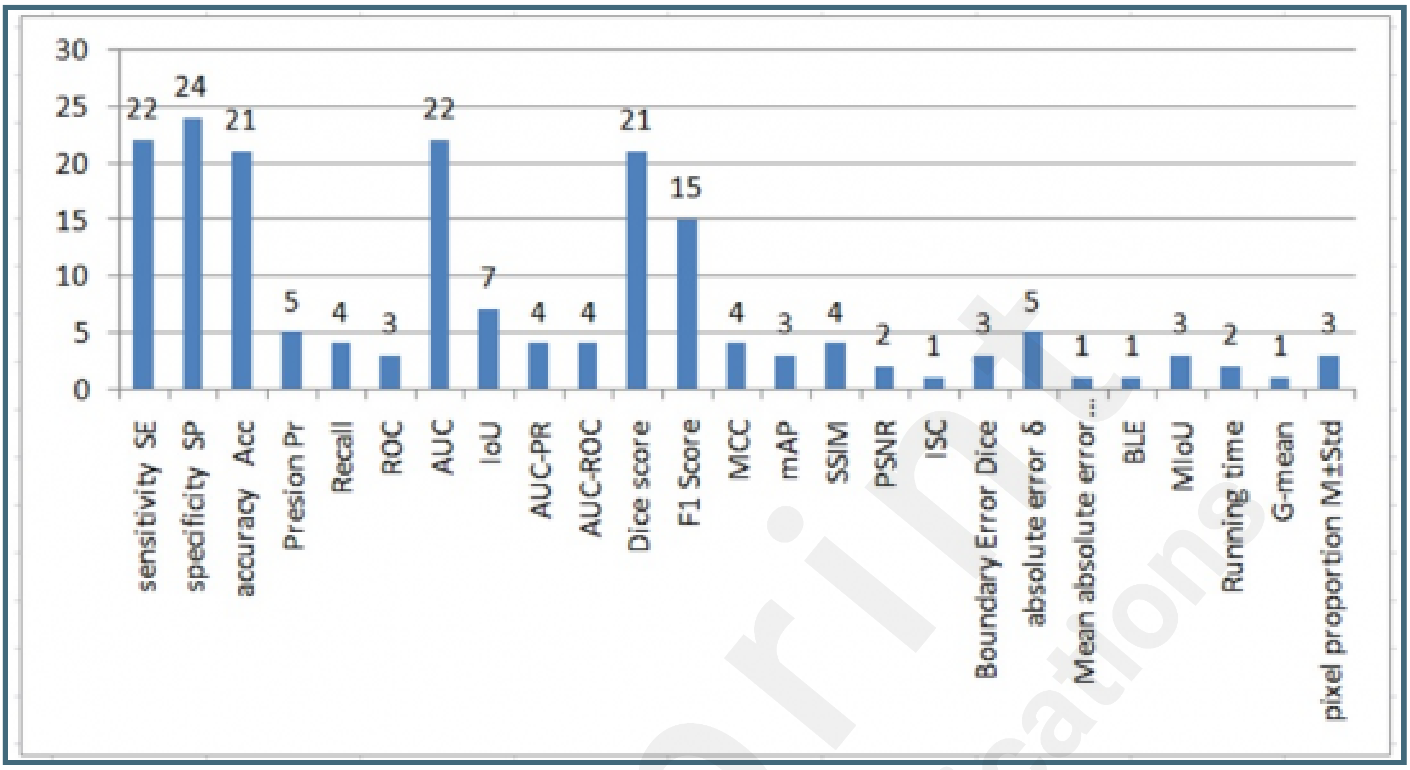
GAN architecture.



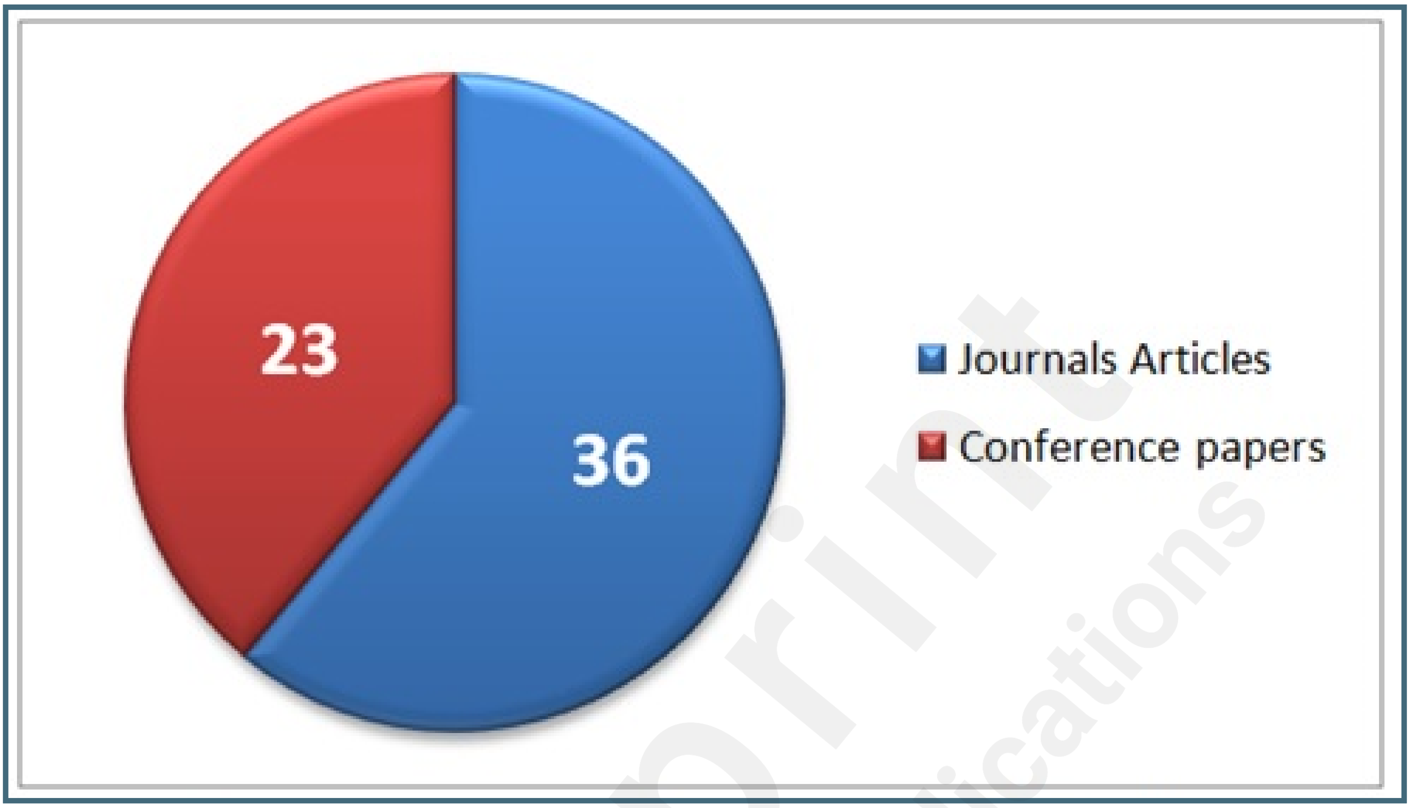
Benefits categories for GANs-based methods on glaucoma screening.



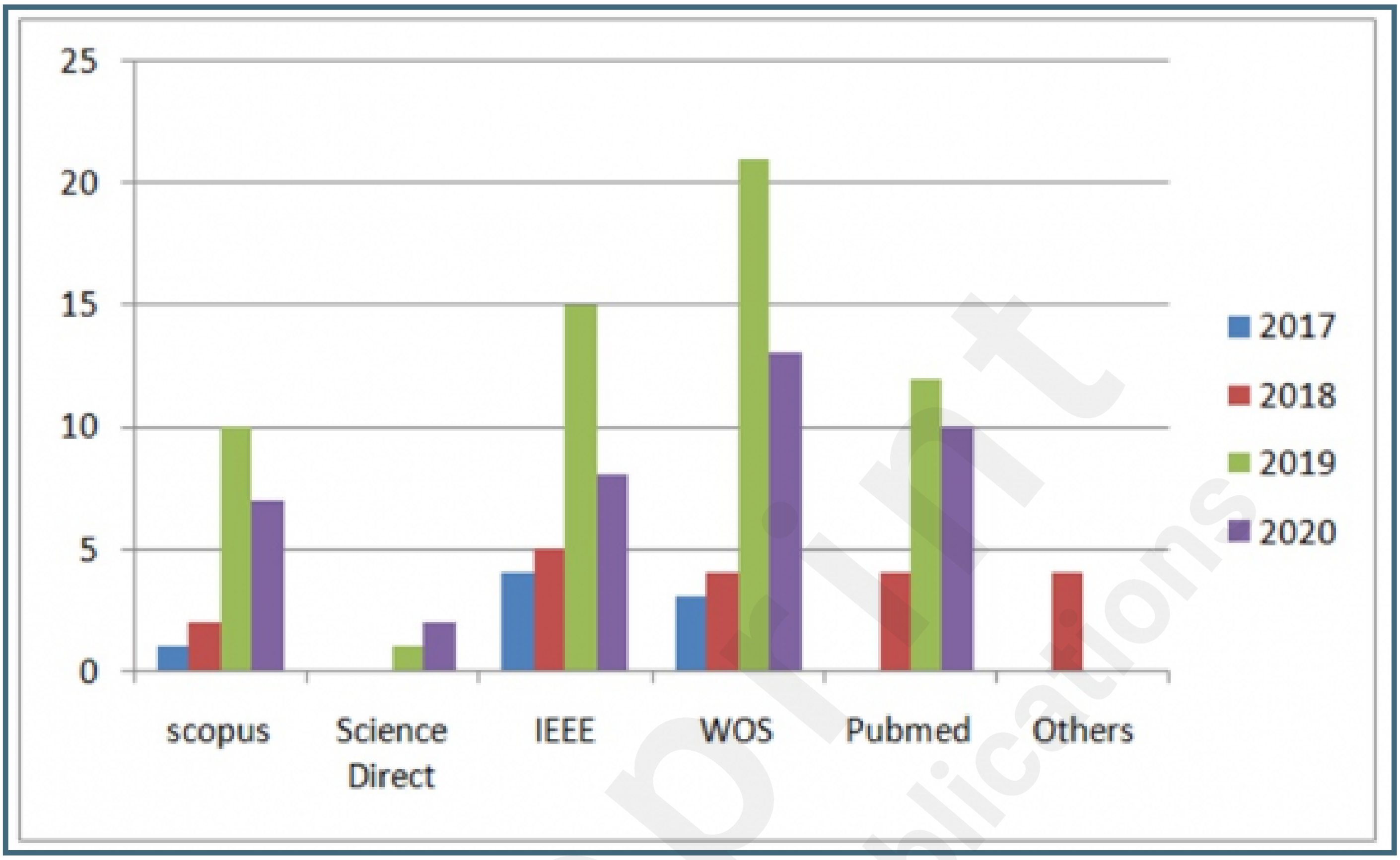
Distribution of frequently used metrics.



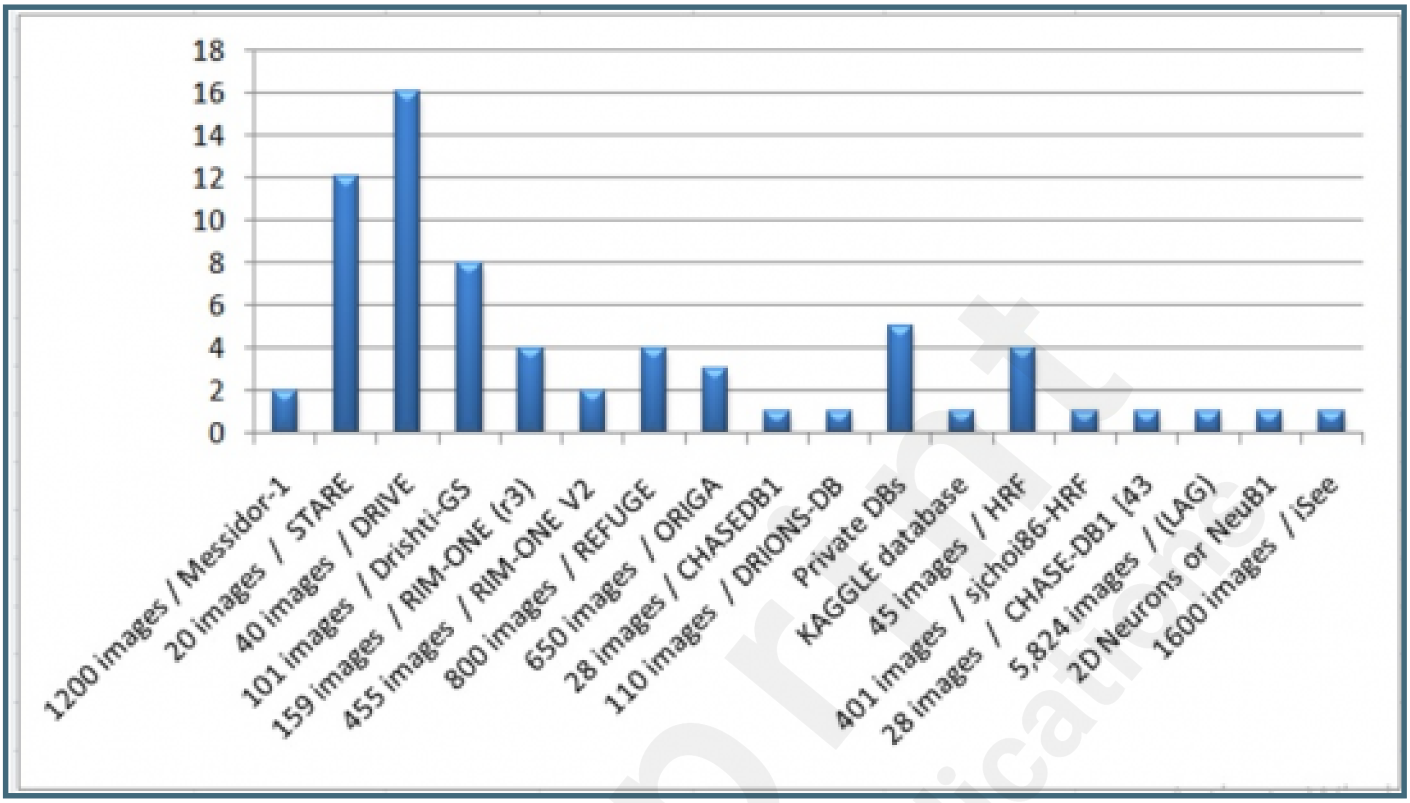
Types of current publications.



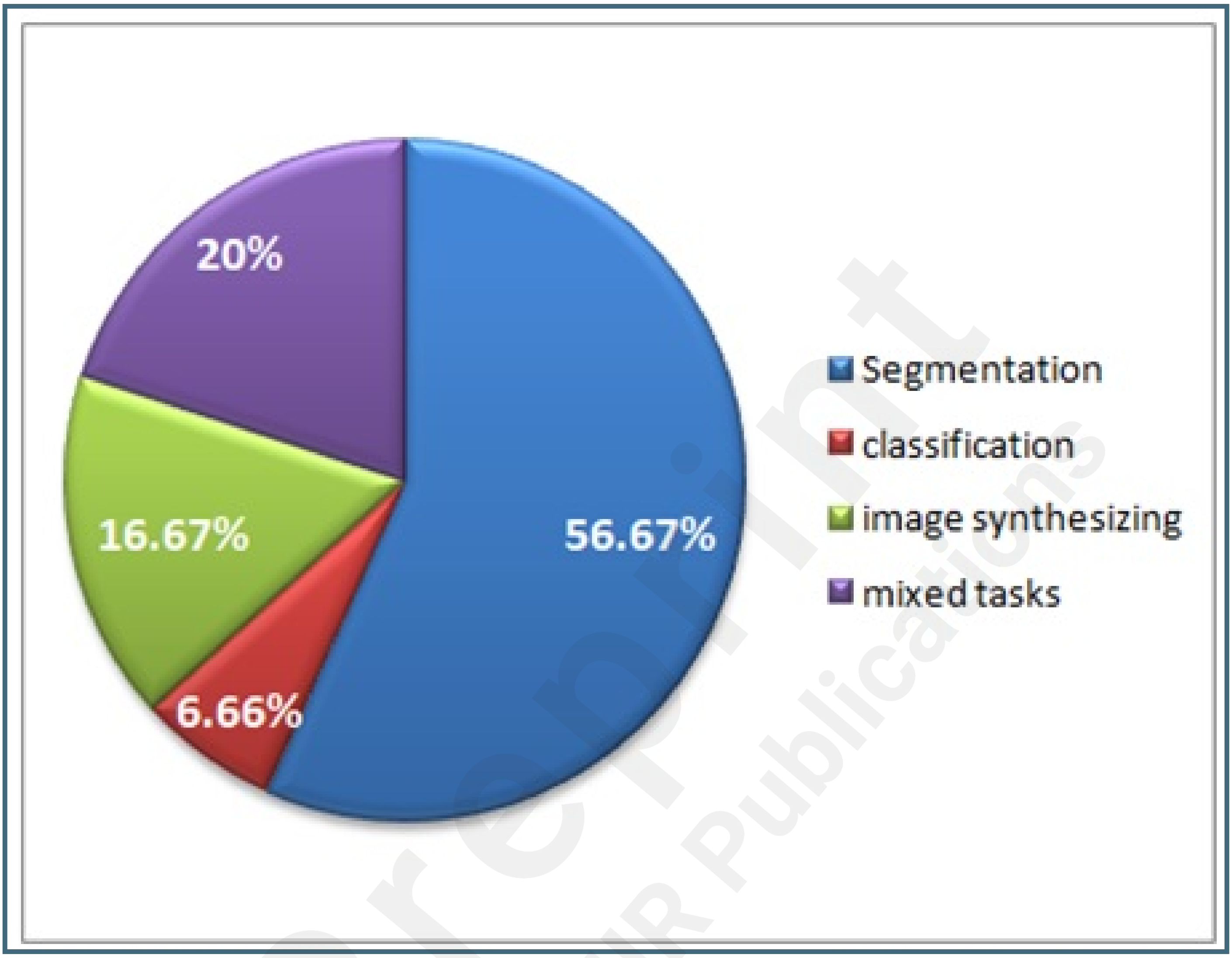
Distribution of papers per libraries.



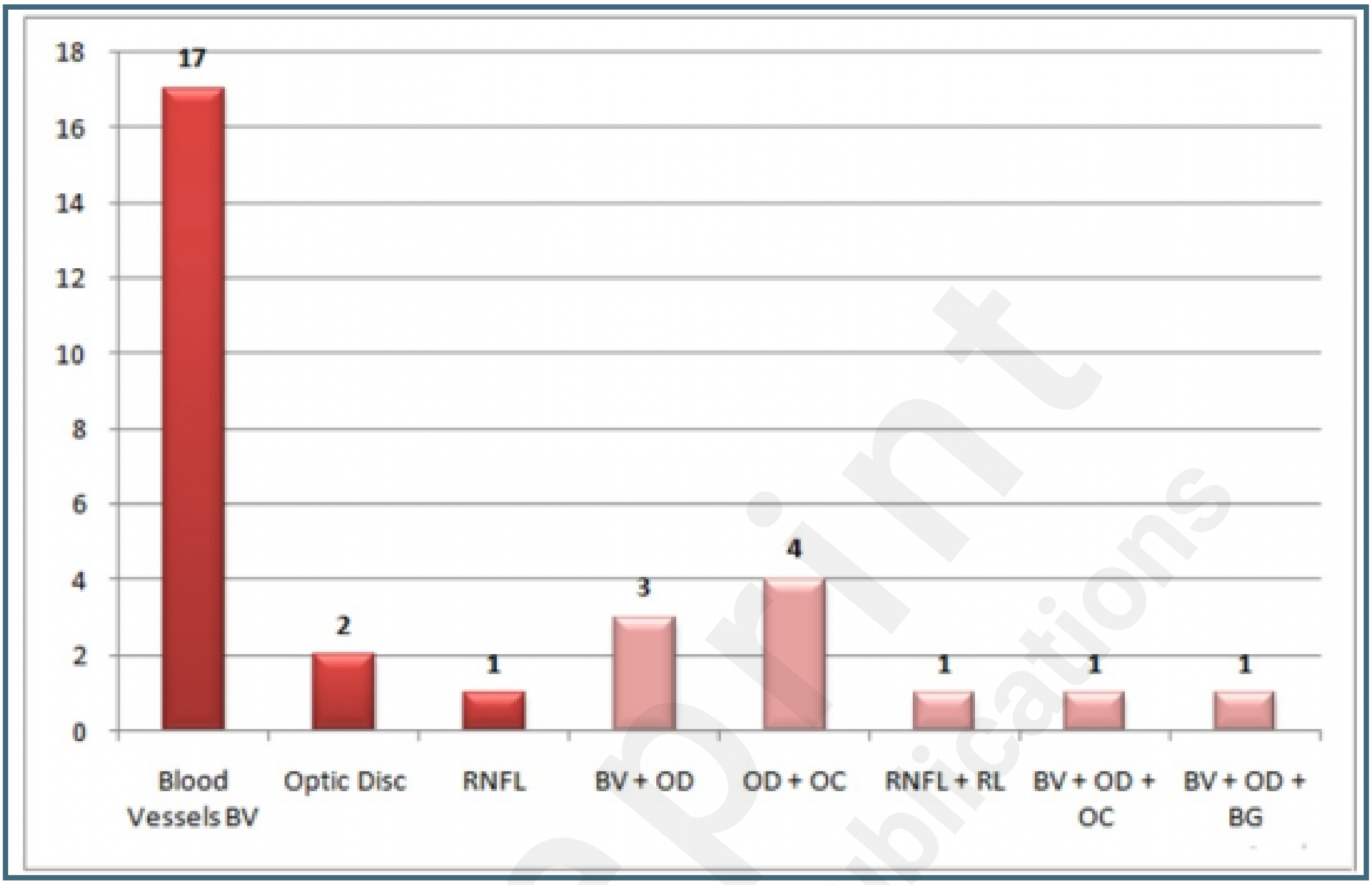
Frequently used datasets.



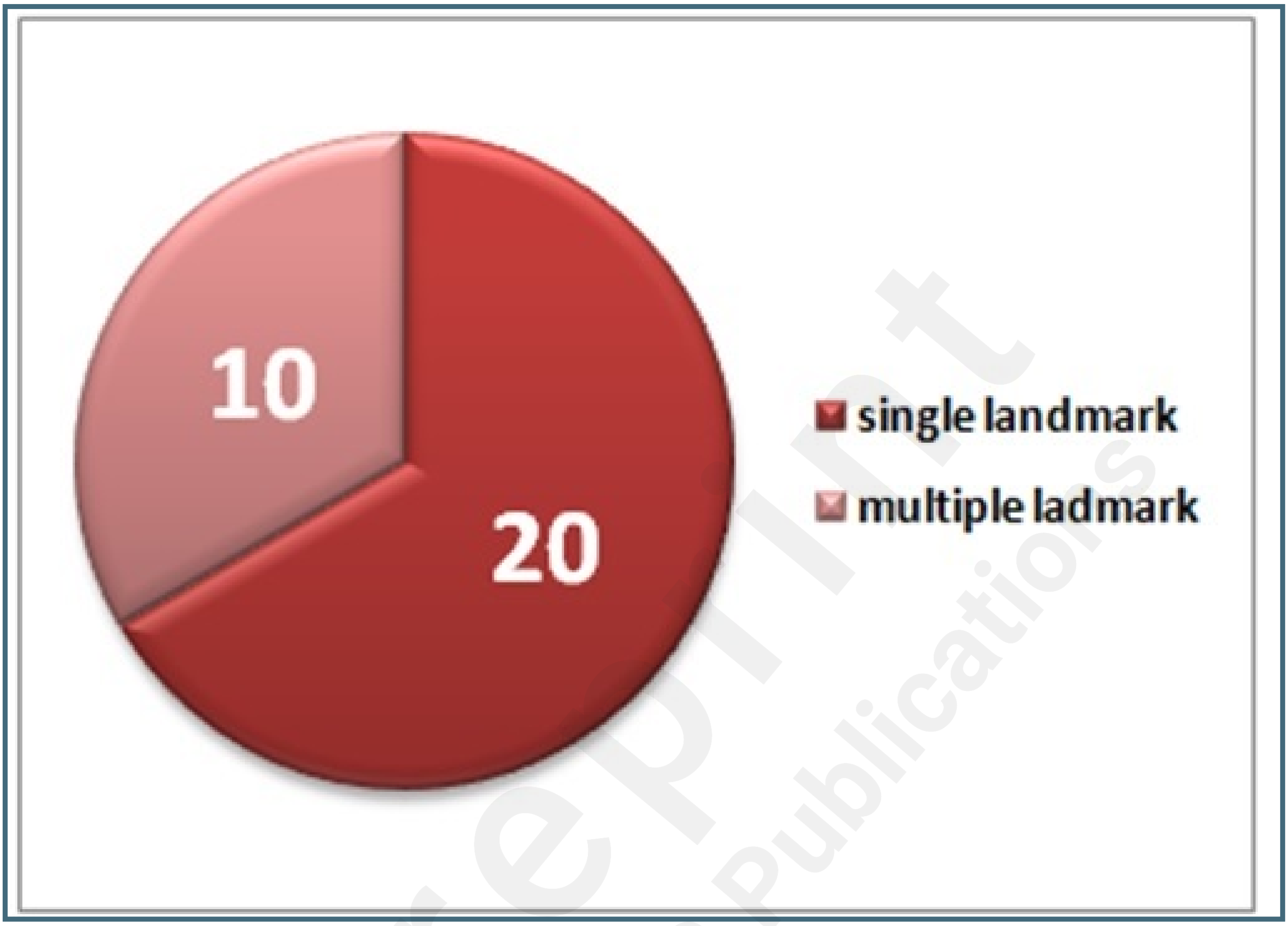
Distribution of papers according to their task.



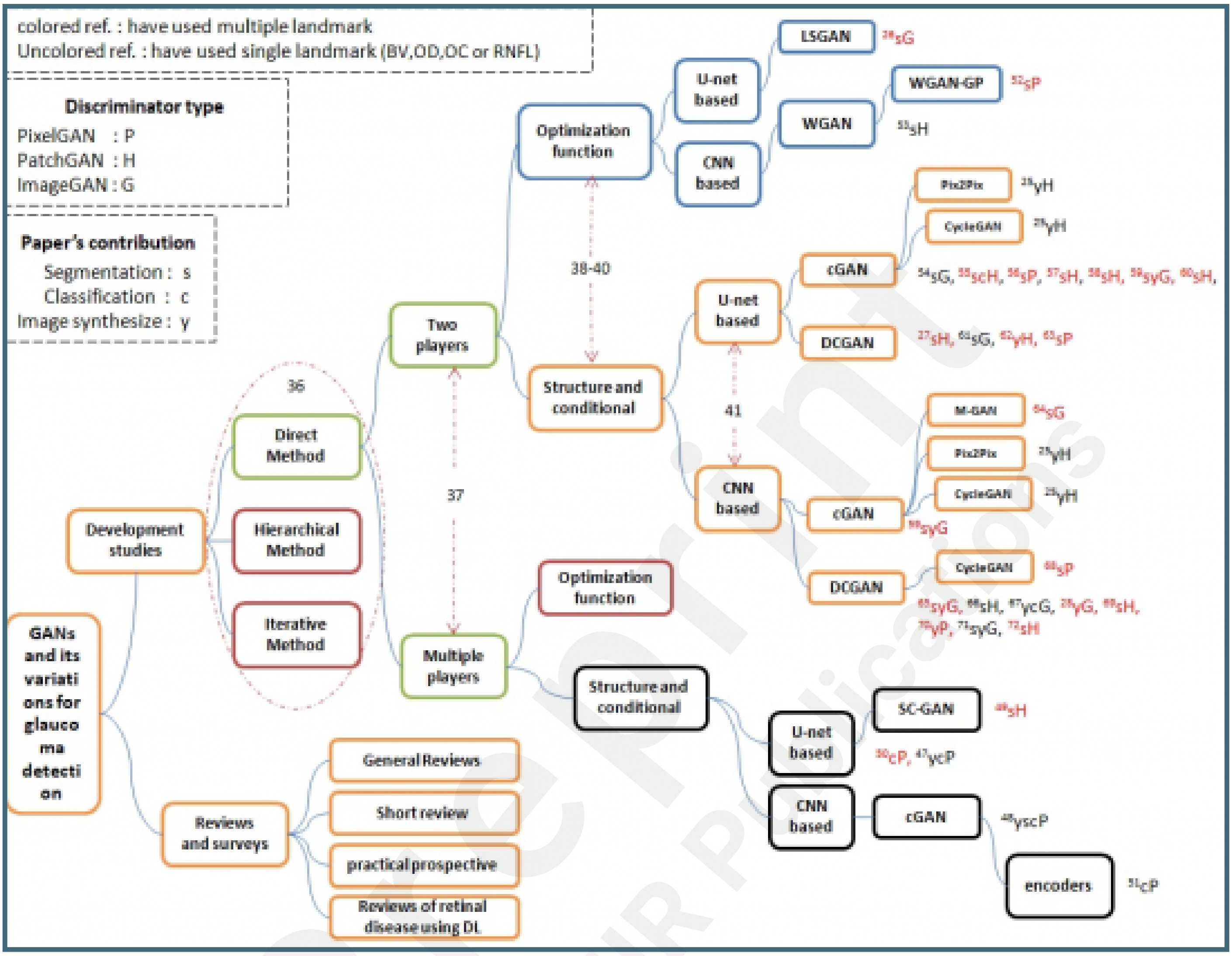
Distribution of papers per each landmark.



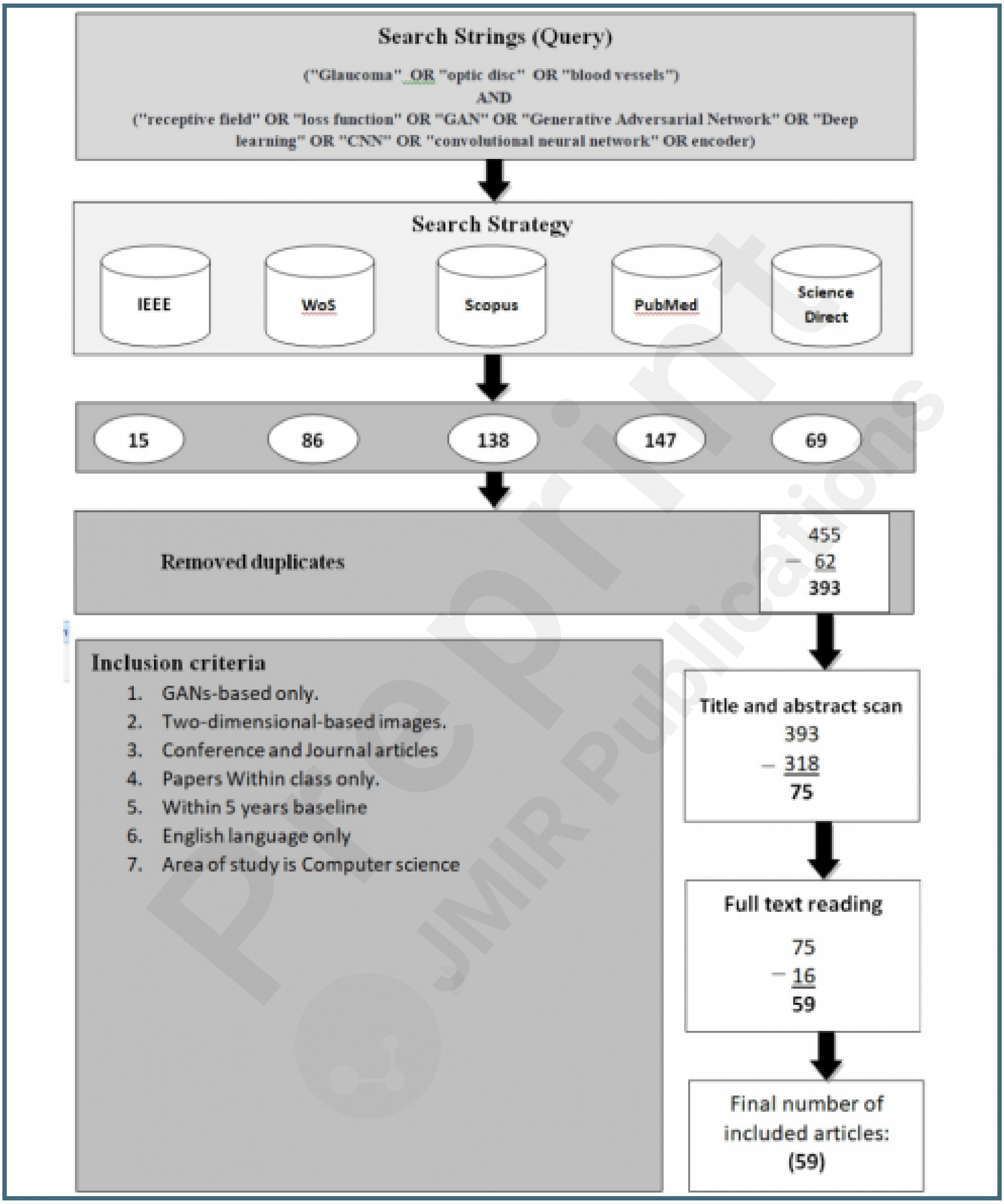
Distribution of paper per using single-multiple landmarks.



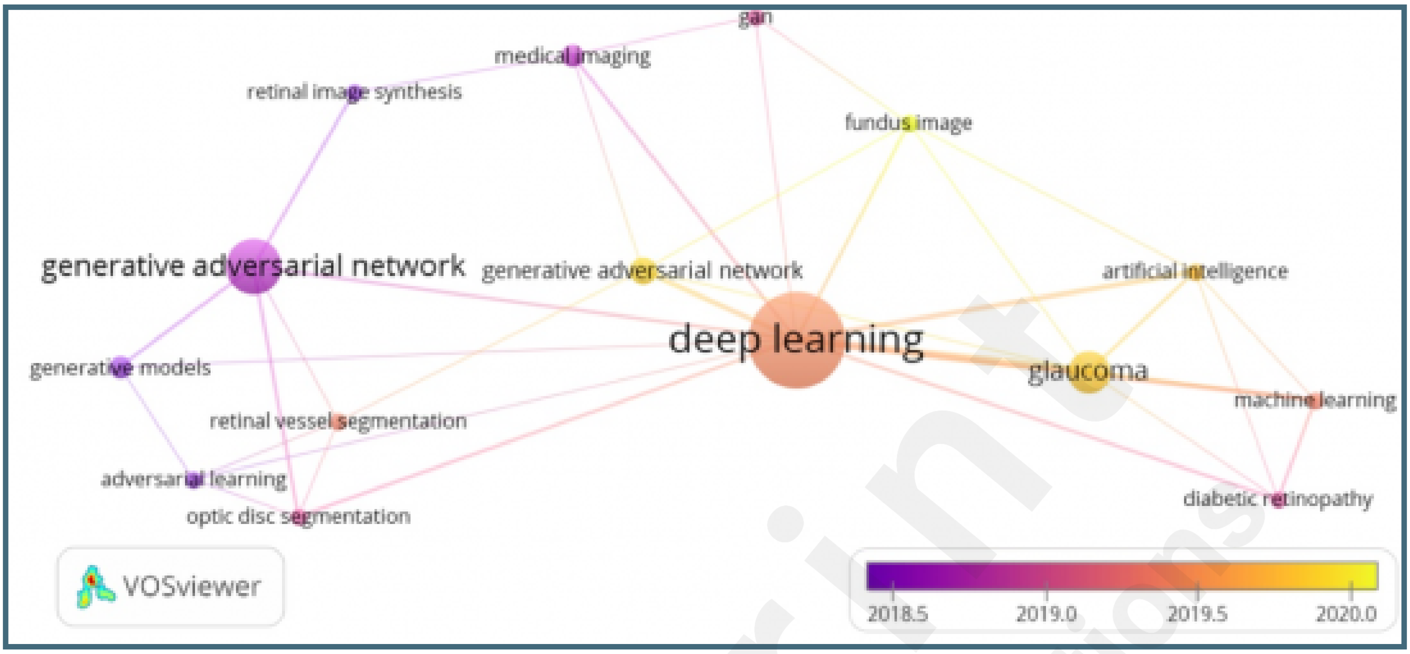
Taxonomy of research literature on Glaucoma screening based GANs technique.



Flowchart of the study selection with the research query and inclusion criteria.



Scope validation diagram.



Multimedia Appendixes

Literature results.
URL: https://asset.jmir.pub/assets/fac49c5f4d6f4723028374ef2f0d296a.pdf

CONSORT (or other) checklists

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H-index, Researcher ID, ORCID, Google Scholar of the authors.
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TOC/Feature image for homepages

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