Clinical Trial Protocol: PRX100.FDAIIb

Protocol Title:	A Single-Center, Double-Masked Evaluation of the Efficacy and Safety of PRX-100 in the Treatment of Early to Moderate Presbyopia
Protocol Number:	PRX100.FDAIIb
Study Phase:	2b
Investigational Product Name:	PRX-100 (aceclidine [redacted] and tropicamide [redacted]) Ophthalmic Solution 120,609
Indication:	Presbyopia
Investigators:	Single Site, Principal Investigator: [redacted]
Sponsor:	Presbyopia Therapies, LLC 915 Ocean Blvd. Coronado, CA 92118
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673 949-542-3882 www.alphairb.com

	Date
Original Protocol:	05Apr2017
Amendment 1:	27Apr2017
Amendment 2:	04May2017
Amendment 3:	11Aug2017
Amendment 4:	29Mar2018
Amendment 5:	03Jul2018

Confidentiality Statement

MEDICAL MONITOR

Medical Monitor:	[redacted]

ORA PERSONNEL

Department Vice President:	[redacted]
Project Manager:	[redacted]

SYNOPSIS

Protocol Title:	A Single-Center, Double-Masked Evaluation of the Efficacy and Safety of PRX-100 in the Treatment of Early to Moderate Presbyopia
Protocol Number:	PRX100.FDAIIb
Investigational Product:	PRX-100 (aceclidine [redacted] and tropicamide [redacted]) Ophthalmic Solution
Study Phase:	2b
Primary Objective(s):	To evaluate the safety and efficacy of PRX-100 compared with aceclidine alone and vehicle in the treatment of early to moderate presbyopia.
Secondary Objective(s):	Not applicable
Overall Study Design:	
Structure:	Single-center, double-masked, randomized, crossover, active and vehicle-controlled, safety and efficacy study
Duration:	Approximately 7 weeks (4 study visits)
Controls:	Vehicle Ophthalmic Solution (for PRX-100)
Dosage/Dose Regimen/ Instillation/Application/ Use:	Study visit 1: All subjects [redacted] Study visit 2, 3, 4: [redacted] All subjects will receive each treatment once (crossover study design). Subjects will be randomized to one of three latin square design sequences detailing the order in which treatments will be administered over the three study visits. • PRX-100 (aceclidine [redacted] and tropicamide [redacted]) Ophthalmic Solution • [redacted] Aceclidine Ophthalmic Solution • PRX-100 Vehicle Ophthalmic Solution
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

Study Population Characteristics:

Number of Subjects: Approximately 60 subjects will be enrolled in order to complete at least 30 study eyes within each treatment arm that have a pre-treatment, baseline monocular best-corrected distance VA at 45 cm between [redacted] in their study eye.

Condition/Disease: Healthy adult subjects ages 48 to 64 years who have presbyopia

Inclusion Criteria: Subjects must:

1. Be able and willing to provide written informed consent and sign Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed;
2. Be able and willing to follow all instructions and attend study visits;
3. Be 48-64 years of age of either sex and any race or ethnicity at visit 1;
4. [redacted]
6. Be an early to moderate presbyope [redacted]
8. Have a negative urine pregnancy test at visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically

sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control;

9. Be able and willing to avoid all disallowed medications for the appropriate washout period and during the study without significant risk to the subject.

Exclusion Criteria:

Subjects must <u>not</u>:

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy;
2. Have known contraindications or sensitivity to the use of any of the study medications(s) or their components;
3. Have an active ocular infection at visit 1 (bacterial, viral or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (eg, moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye;
4. Have moderate or severe dry eye [redacted]
7. [redacted]

10. Have dark-adapted pupillometry measurements of < 4.0 mm in either eye within 3 months of visit 1;
11. Have intraocular pressure (IOP) that is less than 5 millimeters of mercury (mmHg) or greater than 22 mmHg in either eye documented at visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at visit 1;
12. Have abnormal findings on dilated fundus exam in either eye documented within 3 months of visit 1 or a known history of retinal detachment or clinically significant retinal disease in either eye;
13. Have a known history or diagnosis in the past of: iritis, scleritis or uveitis, whether active or inactive;
14. Have had surgical intervention (ocular or systemic) within 6 months prior to visit 1, or planned surgical intervention within 30 days after visit 4;
15. Have undergone refractive eye surgery (incisional keratotomy, photorefractive keratectomy [PRK], laser in situ keratomileusis [LASIK], laser-assisted sub-epithelial keratectomy [LASEK]), corneal inlay procedures, cataract extraction, or intraocular lens placement;
16. Use artificial tears or lubricant eye ointment on a daily basis;

17. [redacted]
18. Have an inability or refuse to discontinue soft contact lens wear 7 days prior to study visit 1 and rigid gas permeable (RGP) contact lens wear 14 days prior to visit 1 and during the study;
19. Use any of the following disallowed medications during the 2 weeks (14 days) prior to visit 1 and during the study:
    a. narcotic (opiate class) pain medication (eg, codeine, OxyContin®, Vicodin®, Tramadol®)
    b. bladder medication (eg Urecholine®, bethanechol)
    c. antipsychotics
    d. antidepressants
    e. attention –deficit/hyperactivity disorder (ADHD) medications
    f. alpha-blockers (eg, tamsulosin, Flomax®, Jayln®, Uroxatral®, Rapaflo®)
    g. anticholinergics (eg, atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl)
    h. muscarinic receptor agonists or cholinergic agonists (eg, Salagen®, Evoxac®)
    i. over-the-counter (OTC) or prescription antihistamines or decongestants
    j. any prescribed topical ophthalmic medications
    k. recreational drug use (eg, marijuana, methadone, heroin, cocaine);
20. Have a diagnosis of diabetes mellitus or a history of elevated blood sugar;
21. Have a condition or a situation, which in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable: cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic,

dermatologic, hematologic, neurologic, or psychiatric disease.

Study Treatments:

- PRX-100 (aceclidine [redacted] and tropicamide [redacted]) Ophthalmic Solution
- [redacted] Aceclidine Ophthalmic Solution
- Vehicle Ophthalmic Solution (for PRX-100)

Evaluation Criteria:

Efficacy Measures:

Primary Efficacy Variable:

- Percentage of subjects who achieve a 3-line (15-letters) or greater improvement from pre-treatment in the measurement of monocular best-corrected distance VA at 45 cm at 1h post-treatment in the study eye.

Secondary Efficacy Variable:

- The percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letters) or greater improvement from pre-treatment by 1-letter increments in the measurement of monocular best-corrected distance VA at 45 cm in the study eye at each time point
    - 0.5, 1, 3, 4, 5 and 7h post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of post-treatment monocular best-corrected distance VA at [redacted] compared to pre-treatment monocular best-corrected distance VA [redacted]
- Mean monocular best-corrected distance logMAR VA at near distances in the study eye
    - Post-treatment assessments compared to pre-treatment assessment
    - Two near testing distances will be assessed: 45 cm (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA at 45

cm compared to pre-treatment binocular best-corrected distance VA at 45 cm
    - 0.5, 1, 3, 4, 5 and 7h post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA [redacted] compared to pre-treatment binocular best-corrected distance VA [redacted]
- Mean binocular best-corrected distance logMAR VA at near distance
    - Post-treatment assessments compared to pre-treatment assessment
    - Two near testing distances will be assessed: 45 cm (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]

Exploratory Efficacy Variables:

- [redacted]

- [redacted]

Safety Measures:

- Best-corrected VA
- Low-luminance best-corrected VA
- Slit lamp biomicroscopy
- Conjunctival redness
- IOP
- Adverse events (AEs) (reported, elicited, and observed)

Other Measures:

- Pupillometry

General Statistical Methods and Types of Analyses

General Considerations:

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, SD, median, min, and max). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.10 significance level.

The study eye, defined in section 8.3.1, will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The primary and monocular secondary efficacy analyses will be conducted in the modified intent-to-treat (mITT) population using statistical models which implicitly impute missing data. The mITT population is defined in section 10.2.1. [redacted]

[redacted] The mITT population will be analyzed as treated and will be used for the primary and monocular secondary efficacy analyses. For primary and monocular secondary analyses, sensitivity analyses will be conducted as follows: if subjects do not meet the mITT criteria at any given visit, their improvement indicator (success or failure) at that visit will be imputed once as failure and once as success thereby testing/validating the implicit generalized estimating equation (GEE) imputation.

For primary and monocular secondary endpoints, sensitivity analyses will be performed using the ITT population with observed data only. Additionally, analysis on the primary efficacy variable will be performed on the per protocol (PP) population defined as all subjects who complete the study without major protocol violations/deviations. The PP population will be analyzed as treated using observed data only.

Exploratory efficacy endpoints will be analyzed for all available data similarly to the primary and secondary endpoints.

Safety analyses will be conducted in the safety population defined as all randomized subjects who received treatment. The safety population will be analyzed as treated.

Sample Size:

This study is expected to complete 30 evaluable subjects in each treatment group within the mITT population. Primary analyses will be evaluated at two-sided alpha levels of [redacted]. The primary endpoint will have 84.7% power if [redacted] of the PRX-100 treatment subjects have at least a 3-line (15-letter) improvement from the pre-dose measurement of best distance corrected VA (monocular assessment) while the vehicle group has [redacted] with a 3-line improvement. With these same assumptions, the study will have 90.1% power to show a difference between treatments if the PRX-100 arm has [redacted] subjects with at least a 3-line improvement.

Primary Efficacy Analysis:

The primary efficacy variable in this study is the percentage of subjects with at least a 3-line (15-letter) improvement from the pre-dose measurement of best-corrected distance VA at 45 cm (monocular assessment) at 1h post-treatment in the study eye. Primary analysis will use the mITT population. The primary analyses will separately compare the PRX-100 arm versus the vehicle arm, and the [redacted] Aceclidine arm versus the vehicle arm. PRX-100 will also be compared against [redacted] Aceclidine as a secondary analysis.

Descriptive statistics will be presented for each time point and distance by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) improvement from pre-dose will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by generalized estimating equation methods. Aspects of the model include:

- Response measure: indicator of whether the subject had at least a 3-line (15-letter) improvement from pre-dose in the monocular assessment of best-corrected distance VA at 45 cm in the study eye.
- Fixed effect explanatory measures: sequence, period, and treatment..

- Random effect measure: subject within sequence, to account for the correlation between treatments and periods within a subject.
- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix in the GEE model.

Standard errors and CIs (80 and 90%) will also be presented for each treatment group and the difference between treatment groups. Separate models will be built for each distance (with 45 cm being primary and [redacted] being secondary) and time points. Pairwise comparisons among treatment groups will also be made at each distance and time point using McNemar's tests.

Secondary Efficacy Analysis:

For the secondary efficacy variable of monocular assessment of best-corrected distance VA, the percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letters) or greater improvement from pre-treatment by 1-letter increments in the measurement of monocular best-corrected distance VA will be evaluated at 45 cm for each time point (0.5, 1, 3, 4, 5 and 7h post-treatment) using the mITT population. Analyses will be repeated using the ITT population.

In addition, [redacted] will be compared to pre-treatment assessments in the study eye.

Descriptive statistics will be presented for each time point and distance as well as for the change from pre-dose at each time point and distance by treatment group. The same logistic regression models developed for the primary analyses will be used to test these secondary endpoints.

For continuous secondary endpoints, similar mixed effect models will be employed. Two-sided one-sample *t*-tests from a mixed effects linear model with binocular best-corrected distance VA at near distance change from pre-dose as the response variable; sequence, period, and treatment as fixed effects; and subject within sequence as a random effect term with a variance component covariance matrix to account for the correlation among measures within a subject using $\alpha = 0.1$. Two-sided 80% and 90% CI will be provided as additional descriptors of the data. Separate models will be constructed for each distance and time point separately. Pairwise comparisons between treatment groups will also be made at each distance and time point using one-sample *t*-tests.

Exploratory Efficacy Analysis:

Exploratory efficacy endpoints will be analyzed for all available data similarly to the primary and secondary endpoints in the mITT population and in the ITT population for sensitivity. All exploratory variables will include percentage based and mean based analyses, similar to the primary and secondary endpoints. Pairwise treatment comparisons will be calculated where possible, along with changes from pre-treatment; otherwise, analyses will be limited to within treatment statistics.

Other Analysis:

Pupil diameter will be analyzed using similar statistical methods to that of the secondary efficacy variable best-corrected distance VA at near distance for each time point separately.

The average of the subject's three study eye pupil diameter measurements assessed at each time point will be used as the unit of analysis.

Summary of Known and Potential Risks and Benefits to Human Subjects

There are currently no marketed aceclidine-tropicamide combination products, and no approved pharmacologic treatments for presbyopia. A 2% concentration of aceclidine was approved in several European countries in 1969 for the treatment of glaucoma, and aceclidine has been used in humans at concentrations of up to 4%. Possible AEs associated with aceclidine include redness or brow ache (Romano 1970, Randazzo et al. 2005). Fewer adverse effects have been reported with aceclidine (no angle closure, fewer subjects reporting pain on instillation, greater comfort with long-term use, and no tachyphylaxis) compared to other miotics, like pilocarpine (Francois and Goes 1977; Romano 1970).

Tropicamide was approved in the U.S. for human use in 1960 to produce mydriasis (pupil dilation) and cycloplegia (paralysis of the ciliary muscle) in order to facilitate diagnostic procedures. It is available in the U.S. in two concentrations, 0.5% and 1.0%. Dosing at these concentrations has been shown to be generally safe and effective. Adverse ocular effects of tropicamide include possible irritation and hypersensitivity (anaphylactic) in some individuals, and light sensitivity or increased IOP.

The concentrations proposed for use in Presbyopia Therapeutics' PRX-100 ophthalmic solution [redacted]

Potential benefits of PRX-100 include its unique ability to chemically dissociate miosis from accommodation. PRX-100 could potentially improve near vision through improved pupil-generated depth of focus with no or only slight accommodative enhancement, without inducing distance blur due to induced myopia or the AEs associated with ciliary contraction that occur with the current generation of miotics. PRX-100 might also correct small to moderate degrees of refractive error, enhance distance vision, reduce symptomatic higher order aberrations, and reduce or eliminate light scatter and glare as may occur due to secondary uncorrected refractive error, pre-existing higher order aberrations, as adverse effects following cataract/refractive surgery (eg, glare after cataract/IOL surgery or loss of acuity and contrast after refractive surgery). PRX-100 will also be instilled bilaterally so that the patients will not have to adjust to monovision in which patients may suffer from problems of depth perception or perceived difficulty with near and distance vision.

TABLE OF CONTENTS

List of Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
AE	adverse event
cd/m^2	candela per square meter
CFR	Code of Federal Regulations
CI	confidence interval
CST	Clinical Trial Suite
eCRF	electronic case report form
D	diopter
EKG	electrocardiogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
ICF	informed consent form
IEC	independent ethics committee
IND	investigational new drug application
IOL	intraocular lens
IOP	intraocular pressure
IP	investigational product
IRB	institutional/independent review board
ITT	intent to treat
LASEK	laser-assisted sub-epithelial keratectomy
LASIK	laser in situ keratomileusis
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MAX	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIN	minimum
mmHg	millimeters of mercury
[redacted]	[redacted]

NCS	not clinically significant
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PP	per protocol
PRK	photorefractive keratectomy
QD	once daily
RGP	rigid gas permeable
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
VA	visual acuity

1 INTRODUCTION

Presbyopia is defined by a loss in the ability of the eye to adjust its focal length so that objects at different distances produce focused images on the retina. As the eye ages, the lens of the eye becomes less able to change shape. Hardening of the lens, along with weakening of the ciliary muscles, plays a major role in the pathogenesis of presbyopia and leads to symptoms such as blurred vision, eye strain and headache after reading or computer use (Truscott 2009; Helmholtz 1855; Ostrin and Glasser 2007; Scarcelli 2011).

Presbyopia affects most people over 45 years of age and continues to worsen until approximately 65 years of age. Based on data from 228 countries, it was estimated that in 2005, presbyopia affected more than 1 billion people worldwide. Presbyopia is projected to increase to 1.78 billion people by 2050. More than half of the people with this condition do not have adequate treatment options, which results in some level of disability when performing tasks that require near visual acuity (Holden 2008).

Current treatments available for presbyopia include the use of reading glasses, contact lenses, or refractive (including laser) or intraocular lens (IOL) surgery. Pharmaceutical therapies have been explored but, thus far, continue to be limited in treating presbyopia without being associated with undesirable adverse effects (Gilmartin 1995).

PRX-100 is an ophthalmic solution that contains a low dose of aceclidine [redacted] and tropicamide [redacted]. Both aceclidine and tropicamide have been used extensively in humans for ophthalmic indications. Aceclidine is a parasympathomimetic miotic agent that is approved for lowering IOP in Europe. In 1969, a 2% solution of aceclidine was approved in several European countries for the treatment of glaucoma. Furthermore, aceclidine has been used at concentrations of up to 4% in humans. Tropicamide is an anticholinergic drug that was approved for human use in the US in 1960. Tropicamide induces mydriasis (pupil dilation) and cycloplegia (paralysis of the ciliary muscle) and is used to facilitate ophthalmic patient examinations. Tropicamide is

available in two concentrations, 0.5% and 1.0%, both of which have been shown to be generally safe and effective. Notably, the concentrations of aceclidine and tropicamide in Presbyopia Therapies PRX-100 ophthalmic solution [redacted]

PRX-100 is intended to be used as a supplement to the current therapies available for presbyopia patients by providing short-term, self-administered correction for daytime near vision. The mechanism of action of PRX-100 is analogous to increasing the depth of focus in a camera by reducing the F-stop (higher F stop values, smaller aperture) and taking advantage of "pinhole optics." It is anticipated that PRX-100 will improve near vision by creating miosis (pupil constriction) without induced myopia (blurred distant vision) or adverse effects such as ciliary spasm or brow ache that can be associated with other miotics (Francois and Goes 1977). PRX-100 also has the potential to reduce adverse effects that follow a number of ophthalmic surgical procedures such as: glare after cataract or intraocular lens (IOL) surgery and loss of acuity and contrast after refractive surgery.

2 STUDY OBJECTIVES

The objective of the study is to evaluate the safety and effectiveness of PRX-100 compared with aceclidine alone and vehicle in the treatment of early to moderate presbyopia.

3 CLINICAL HYPOTHESES

The clinical hypothesis is that PRX-100 (the combination of aceclidine and tropicamide) is superior to aceclidine alone and vehicle in improving near vision in subjects with presbyopia.

4 OVERALL STUDY DESIGN

This is a 4-visit randomized, double-masked, single-center, crossover study evaluating the safety and efficacy of PRX-100 compared with aceclidine and vehicle in approximately 60 subjects with early to moderate presbyopia. [redacted]

- PRX-100 (aceclidine [redacted] and tropicamide [redacted]) Ophthalmic Solution
- [redacted] Aceclidine Ophthalmic Solution
- Vehicle Ophthalmic Solution (for PRX-100)

Subjects will be randomized at visit 2 for which treatment will be administered at each study visit. One treatment will be administered at visit 2, 3, and 4. All subjects will receive each treatment once (crossover study design).

4.1 Study Eye Definition

Dynamic Study Eye: One eye per subject will be designated as the study eye at each visit. The study eye will be the eye that meets all the inclusion criteria and none of the exclusion criteria. [redacted]

Static Study Eye: A definition of the study eye based on the Visit 1 measures.

Dynamic study eye will be used with mITT population and the static study eye will used with other populations.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 60 subjects will be enrolled in order to complete at least 30 study eyes within each treatment arm that have a pre-treatment, baseline monocular best-corrected distance VA at [redacted] in their study eye.

5.2 Study Population Characteristics

Healthy adult subjects between 48 and 64 years of age with presbyopia who do not have any conditions, in the Investigator's opinion, which may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation. [redacted]

5.3 Inclusion Criteria

Subjects must:

1. Be able and willing to provide written informed consent and sign Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed;
2. Be able and willing to follow all instructions and attend study visits;
3. Be 48-64 years of age of either sex and any race or ethnicity at visit 1;
4. [redacted]
8. Have a negative urine pregnancy test at visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control;
9. Be able and willing to avoid all disallowed medications for the appropriate washout period and during the study without significant risk to the subject.

5.4 Exclusion Criteria

Subjects must not:

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy;
2. Have known contraindications or sensitivity to the use of any of the study medications(s) or their components;
3. Have an active ocular infection at visit 1 (bacterial, viral or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (eg, moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye;
4. Have moderate or severe dry eye [redacted]

5. [redacted]

10. Have dark-adapted pupillometry measurements of < 4.0 mm in either eye within 3 months of visit 1;
11. Have intraocular pressure (IOP) that is less than 5 millimeters of mercury (mmHg) or greater than 22 mmHg in either eye documented at visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at visit 1;
12. Have abnormal findings on dilated fundus exam in either eye documented within 3 months of visit 1 or a known history of retinal detachment or clinically significant retinal disease in either eye;
13. Have a known history or diagnosis in the past of: iritis, scleritis or uveitis, whether active or inactive;
14. Have had surgical intervention (ocular or systemic) within 6 months prior to visit 1, or planned surgical intervention within 30 days after visit 4;
15. Have undergone refractive eye surgery (incisional keratotomy, photorefractive keratectomy [PRK], laser in situ keratomileusis [LASIK], laser-assisted sub-epithelial keratectomy [LASEK]), corneal inlay procedures, cataract extraction, or intraocular lens placement;
16. Use artificial tears or lubricant eye ointment on a daily basis;
17. [redacted]
18. Have an inability or refuse to discontinue soft contact lens wear 7 days prior to study visit 1 and rigid gas permeable (RGP) contact lens wear 14 days prior to visit 1 and during the study;
19. Use any of the following disallowed medications during the 2 weeks (14 days) prior to visit 1 and during the study:
    a. narcotic (opiate class) pain medication (eg, codeine, OxyContin®, Vicodin®, Tramadol®)

b. bladder medication (eg Urecholine®, bethanechol)
c. antipsychotics
d. antidepressants
e. attention –deficit/hyperactivity disorder (ADHD) medications
f. alpha-blockers (eg, tamsulosin, Flomax®, Jayln®, Uroxatral®, Rapaflo®)
g. anticholinergics (eg, atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl)
h. muscarinic receptor agonists or cholinergic agonists (eg, Salagen®, Evoxac®)
i. over-the-counter (OTC) or prescription antihistamines or decongestants
j. any prescribed topical ophthalmic medications
k. recreational drug use (eg, marijuana, methadone, heroin, cocaine);

20. Have a diagnosis of diabetes mellitus or a history of elevated blood sugar;
21. Have a condition or a situation, which in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable: cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.

5.5 Withdrawal Criteria (if applicable)

Subjects will be withdrawn from the study if any of the following criteria are met:

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy; tests positive to a urine pregnancy test at visit 2, 3 or 4; or refuses to use an adequate method of contraception for the duration of the study;

2. Have an active ocular infection at visit 2, 3 or 4 (bacterial, viral or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (eg, moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye.

Subjects may also be withdrawn from the study for the following reasons:

- AE
- Lost to follow-up
- Withdrawal of consent by subject
- Investigator discretion
- Death
- Subject not following required study procedures

- Study terminated by the Sponsor
- Other

Subject withdrawals will be documented clearly on the subject's source document.

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variable

- Percentage of subjects who achieve a 3-line (15-letters) or greater improvement from pre-treatment in the measurement of monocular best-corrected distance VA at 45 cm at 1h post-treatment in the study eye.

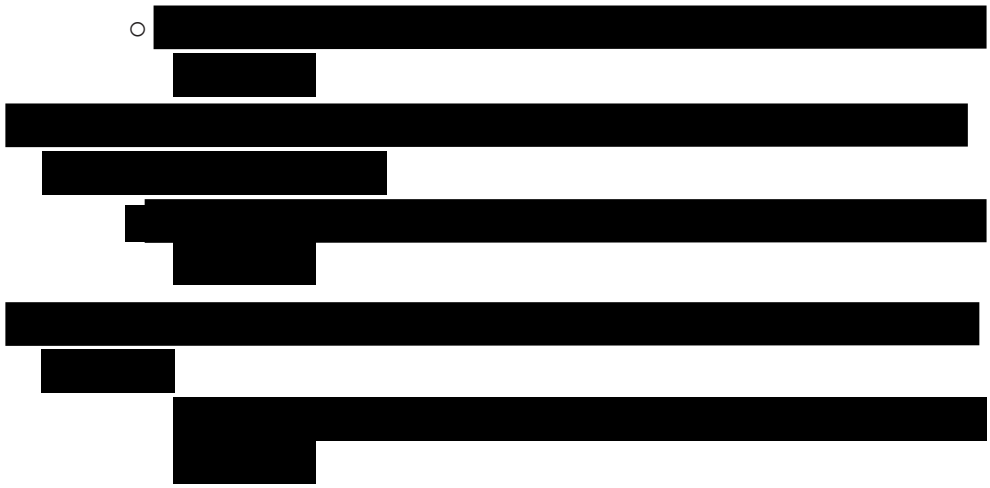
6.1.2 Secondary Efficacy Variable

- The percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letters) or greater improvement from pre-treatment by 1-letter increments in the measurement of monocular best-corrected distance VA will be evaluated at 45 cm for each time point
    - 0.5, 1, 3, 4, 5 and 7h post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of post-treatment monocular best-corrected distance VA at [redacted] compared to pre-treatment monocular best-corrected distance VA at [redacted]
- Mean monocular best-corrected distance logMAR VA at near distances in the study eye
    - Post-treatment assessments compared to pre-treatment assessment
    - Two near testing distances will be assessed: 45 cm (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA at [redacted] compared to pre-treatment binocular best-corrected distance VA at [redacted]

- [redacted]
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA at [redacted] compared to pre-treatment binocular best-corrected distance VA at [redacted]
- Mean binocular best-corrected distance logMAR VA at near distance
  - Post-treatment assessments compared to pre-treatment assessment
  - Two near testing distances will be assessed: 45 cm (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]

6.1.3 Exploratory Efficacy Variables:

- [redacted]



6.1.4 Criteria for Effectiveness

Changes in best-corrected distance VA at near distance will be calculated as the difference, in logMAR units, between the post-treatment monocular (study eye) and binocular best-corrected distance VA measurements at near (45 cm and [redacted] minus the pre-treatment monocular (study eye) and binocular best-corrected distance VA measurements at near (45 cm and [redacted] A 3-line improvement in VA is considered clinically meaningful.

6.2 Safety Measures

- Urine pregnancy test
- Best-corrected distance VA
- Low-luminance best-corrected distance VA
- Slit-lamp biomicroscopy
- Conjunctival redness
- IOP
- AEs (reported, elicited, and observed)

6.3 Other Measures

- Pupillometry

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)

The study treatments are as follows:

- PRX-100 (Aceclidine [redacted] and Tropicamide [redacted]) Ophthalmic Solution
- [redacted] Aceclidine Ophthalmic Solution
- Vehicle Ophthalmic Solution (for PRX-100)

[redacted]

For the PRX-100 Ophthalmic Solution study treatment arm, the tropicamide solution will be used as a diluent to re-constitute the aceclidine lyophilized powder and the re-constituted solution will be administered to study participants.

For the [redacted] aceclidine ophthalmic solution treatment arm, a separate diluent formulation that does not contain tropicamide will be used to re-constitute the aceclidine lyophilized powder and the re-constituted solution will be administered to study participants.

A third solution, vehicle ophthalmic solution (for PRX-100), will be provided for the vehicle treatment arm. The formulation composition will be identical to that of the re-constituted PRX-100 ophthalmic solution except it will not contain tropicamide or aceclidine active ingredient. There will be no re-constitution step for the vehicle treatment arm.

7.1.2 Instructions for Use and Administration

- [redacted]

- Both the technician who administers the treatment and the subject will be masked to the treatment identity.

7.2 Other Study Supplies

- Clarity HCG (RAC Medical Boca Raton, FL) will be used for pregnancy tests
- Fluorescein sodium ophthalmic strips, USP
- Saline

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Section 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e. changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted IRB.

8.1.3 Washout Intervals

- Narcotic (opiate class) pain medication (eg, codeine, oxycontin, Vicodin®, Tramadol®): 2 weeks
- bladder medication (eg, Urecholine®, Bethanechol®): 2 weeks
- Antipsychotics: 2 weeks
- Antidepressants: 2 weeks
- Anticholinergics (eg, atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl): 2 weeks

- Muscarinic receptor agonists or cholinergic agonists (eg, Salagen®, Evoxac®): 2 weeks
- Over-the-counter and prescription antihistamines or decongestants: 2 weeks
- Artificial tears: on the day of or during visit 1, 2, 3 or 4
- Any prescribed topical ophthalmic medications: 2 weeks

8.1.4 Procedures for Final Study Entry

Subjects must satisfy all inclusion and none of the exclusion criteria in order to be entered into the study.

8.1.5 Pregnancy

Females must have a negative urine pregnancy test at visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

In the event a female has a positive urine pregnancy test at visit 2, 3 or 4, the subject will be withdrawn from the study and the Investigator will notify Ora and the sponsor within 24 hours of knowledge of the event.

8.1.6 Methods for Assignment to Treatment Groups:

Each subject who signs an informed consent form will be assigned a screening number. Screening numbers will be assigned in sequential order beginning with 001. Once a subject meets all qualification criteria, he/she will be randomized in a 1:1:1 ratio to one of three Latin square design sequences [(1,2,3), (2,3,1), and (3,1,2)] detailing the order in which treatments (1: PRX-100, 2: aceclidine, 3: vehicle) will be administered over the three study visits and will be assigned a 4-digit subject number. Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

A trained technician will be instructed to administer the appropriate bottle of study drug at visits 2, 3 and 4 that corresponds to the assigned subject number according to the randomization list.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter taken within 30 days of the study visit, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

All current and prior ocular medical and surgical history is to be recorded on the subject's source document and corresponding eCRF. All current and prior significant general medical and surgical history is to be recorded on the subject's source document and corresponding eCRF.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Washout intervals as described in Section 8.1.3 should be followed for all prohibited medications. Soft contact lenses must be removed at least 7 days prior to study visit 1 and during the study and rigid gas permeable (RGP) contact lenses must be removed at least 14 days prior to study visit 1 and during the study.

8.2.2 Escape Medications

Not applicable

8.2.3 Special Diet or Activities

Not applicable

8.3 Examination Procedures

8.3.1 Procedures to be performed at the Study Visit with Regard to Study Objective(s)

Visit 1 (Day 1)

- Informed consent and HIPAA
- Demographics
- Medical/medication history
- Urine pregnancy test (for females of child-bearing potential)
- Inclusion/exclusion criteria review
- Screening assessments:
    - Screening monocular best-corrected distance visual acuity (VA) at 45 cm*
    - Screening monocular best-corrected distance VA*
- Slit-lamp biomicroscopy
- Fluorescein staining
    - *Subjects should wait at least 30 minutes with his/her eyes closed following fluorescein staining* [redacted]

Visits 2, 3, 4 (Days 15±7, 29±7, 43±7)

- Medical and medication history update
- Urine pregnancy test (for females of child-bearing potential)
- Subjects will be asked to read printed instructions about what will be completed at each visit prior to beginning baseline/pre-treatment assessments.
- Baseline/pre-treatment assessments:
    - Pupillometry [redacted]
    - Monocular best-corrected distance VA at [redacted]
    - Binocular best-corrected distance VA at [redacted]
    - Monocular best-corrected distance visual acuity at [redacted] *
    - Binocular best-corrected distance VA at [redacted]

- Monocular best-corrected distance VA*
- Binocular best-corrected distance VA*
- Monocular low-luminance best-corrected distance VA*
- Binocular low-luminance best-corrected distance VA*
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness assessment

- Randomization will occur at visit 2 for all qualified subjects. All randomized subjects will receive each treatment once at each visit 2, 3 and 4 (crossover study design). Subjects randomization will dictate which treatment will be administered at each study visit.

Treatment Administration

- Instillation of PRX-100, aceclidine, or vehicle OU
  - [redacted]

Post-treatment assessments**

- AE query post-treatment and 1 hour post-treatment
- The following assessments will be made 0.5, 1, 3, 4, 5 and 7 hours post-treatment:
  - Conjunctival redness assessment
  - Pupillometry [redacted]
  - Monocular best-corrected distance VA at [redacted]
  - Binocular best-corrected distance VA at [redacted]
  - Monocular best-corrected distance VA*

        - Binocular best-corrected distance VA*
        - Monocular low-luminance best-corrected distance VA*
        - Binocular low-luminance best-corrected distance VA*
    - The following assessments will be made 1, 4 and 5 hours post-treatment:
        - Monocular best-corrected distance VA at [redacted]
        - Binocular best-corrected distance VA at [redacted]
        - All best-corrected distance VA at [redacted] assessments to be assessed immediately following best-corrected distance VA at 45 cm assessments
    - The following assessments will be made 1 and 5 hours post-treatment following binocular low-luminance best-corrected distance VA:
        - [redacted]
    - Following the 7-hours post-treatment assessments:
        - Slit lamp biomicroscopy
        - IOP
        - AE query

Assessment for Study Exit

- Subjects will be assessed for study exit. Study exit can occur at either visit 1, 2, 3, or 4. If a subject completes the study, Study exit will occur at Visit 4.

* VA to be assessed with best distance correction [redacted]

** Best effort will be made to adhere to [redacted] assessment time points. No minimum/maximum windows are defined for any post-treatment assessment time point.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visit

Refer to Appendix 1 for a schedule of measurements at the Visit.

8.4.2 Unscheduled Visits

In the case of an AE, an Unscheduled Visit may be performed by the Investigator. Unscheduled Visit assessments can include any of the following:

- Medical/medication history
- Urine pregnancy test
- VA assessments
- Slit-lamp biomicroscopy
- Conjunctival redness
- IOP
- Fluorescein staining
- AE query

The Investigator may perform additional assessments, if needed. All additional assessments will be documented in the subject's source document.

8.5 Compliance with Protocol

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s), such as Food and Drug Administration (FDA) GCP Regulations and Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312, as appropriate.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 5.5.

8.6.3 Discontinued Subjects

A discontinued subject is one who does not complete the four (4) protocol defined study visits. A subject MAY be discontinued at the discretion of the Investigator, Sponsor, and/or the IRB/IEC. Subjects will also be discontinued if the following criteria is met:

- [redacted]

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events (AEs) will be followed as described in Section 9.

8.7 Study Termination

The study may be terminated at any time by the Investigator, the sponsor, and/or Ora with appropriate notification.

8.8 Study **Duration**

This study is comprised of 4 visits over a total duration of approximately 7 weeks.

8.9 **Monitoring and Quality Assurance**

During the course of the study an Ora, Inc. monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora, Inc. quality assurance and/or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 **Adverse Event**

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. An AE

can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, without any judgment about causality. An AE can arise from any use of the investigational product (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, patient characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release) associated with a medical device.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the subject's source document and eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to investigational product, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

All AEs will be collected from the time a subject signs the informed consent form through the subject's study exit visit.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the investigational product should be determined by the Investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the investigational product caused the AE.

- *Not Suspected*: A reasonable possibility does not exist that the investigational product caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational product-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the investigational product using these explanations:

- *Unexpected*: an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.

- *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.

- *Not applicable:* an AE unrelated to the investigational product.

Adverse events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
    - Note: An AE is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
    - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.
    - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the study sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate subject source document and eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

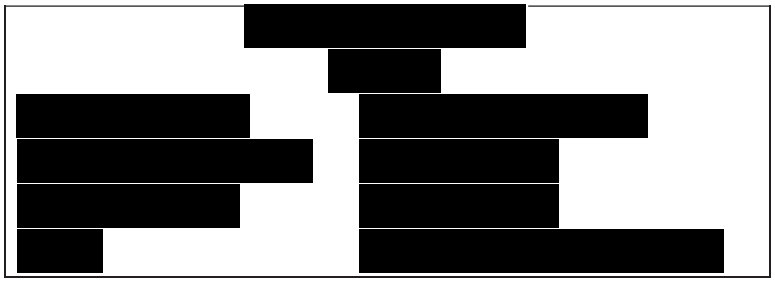
All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the study sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the investigational product, must be immediately reported by the Investigator to Ora and the sponsor within 24 hours of becoming aware of the event. All information relevant to the SAE must be recorded on the appropriate source document, SAE Report Form and eCRF. The Investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to the information reported on the source document, SAE Report Form and eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the Investigator must notify Ora and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the investigational product; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:



9.4 Procedures for Unmasking (if applicable)

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking investigational product. A two-panel clinical label with scratch offs will be used for unmasking.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The Investigator will follow unresolved AEs to resolution, until the subject is lost to follow-up or until the AE is otherwise explained. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the source document with the status noted.

If the Investigator becomes aware of any new information regarding a SAE (i.e. resolution, change in condition, or new treatment), a new Serious Adverse Event Report Form must be completed and faxed to Ora and/or the study sponsor within 24 hours. The original SAE Report Form is not to be altered. The Report Form should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 General Considerations

All quantitative/continuous study assessments will be summarized by treatment (or treatment sequence) and visit and time point (as applicable) using descriptive statistics (n, mean, SD, median, minimum, and maximum. All qualitative/categorical study assessments will be summarized by treatment (or treatment sequence), visits, and time point (as applicable) using frequency counts and percentages.

Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.10 significance level. When applicable, two-sided 80% and 90% CIs will be reported. All p-values (*P*) will be displayed to four decimal places, with *P* less than 0.0001 presented as '< 0.0001' and *P* greater than 0.9999 presented as '> 0.9999'.

Differences between PRX-100 and [redacted] Aceclidine versus vehicle will be calculated as active – vehicle. Differences between PRX-100 versus [redacted] Aceclidine will be calculated as PRX-100 – [redacted] Aceclidine.

All study data will be listed by subject, treatment, and time point (as applicable).

The study eye, [redacted] will be used for all monocular analyses. The fellow eye will be inherently included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The primary and monocular secondary efficacy analyses will be conducted in the modified intent-to-treat (mITT) population. The mITT population is defined in Section 10.2.1. [redacted]. The mITT population will be analyzed as treated and will be used for the primary and monocular secondary efficacy analyses. For primary and monocular secondary analyses, sensitivity analyses will be conducted as follows: if subjects do not meet the mITT criteria at any given visit, their improvement indicator (success or failure) at that visit will be imputed once as failure and once as success thereby testing/validating the implicit generalized estimating equation (GEE) imputation.

Sensitivity analyses on the primary efficacy variable will be performed using the ITT population with observed data only to assess robustness of the results from the mITT population. Additionally, analysis on the primary efficacy variable will be performed on the per protocol (PP) population defined as all subjects who complete the study without major protocol violations/deviations. The PP population will be analyzed as treated using observed data only.

Primary, secondary, and exploratory efficacy endpoints will be analyzed for all available data as treated. If a subject receives a particular treatment on more than 1 visit the second visit will not be used in efficacy analyses.

Safety analyses will be conducted in the safety population defined as all randomized subjects who received treatment. The safety population will be analyzed as treated. If a subject receives a particular treatment on more than 1 visit, data from both visits will be used in the safety analyses. Data from both visits will be averaged for continuous data and worse value will be used for categorical data.

10.2 Study Populations

10.2.1 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population consists of the study eye with baseline/pre-treatment monocular best-corrected distance VA [redacted] measure for each visit of all subjects who are

randomized. [redacted] The mITT population will be analyzed as treated and will be the primary population used for the primary and monocular secondary efficacy analyses.

Pairwise comparisons between treatment groups and changes from pre-treatment will use the mITT population using only those study eyes which have baseline/pre-treatment monocular best-corrected distance VA at [redacted] Because inclusion in the mITT is assessed at each treatment visit separately it is possible subjects are included at some visits/treatments but not at others.

10.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all subjects who are randomized. All data will be included and no subjects will be excluded because of protocol violations/deviations. The ITT population will be analyzed as randomized and will be used for the sensitivity analyses on the primary and secondary monocular efficacy endpoints. The ITT population will be the primary population used to assess the secondary binocular efficacy endpoints.

10.2.3 Per Protocol Population

The Per Protocol (PP) population is a subset of the ITT population and includes subjects with no major protocol violations/deviations likely to affect the primary efficacy endpoint. This population will be analyzed as treated using observed data only for confirmatory and sensitivity analyses.

10.2.4 Safety Population

The safety population includes all randomized subjects who receive at least one dose of study medication. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

10.2.5 Exploratory Population

Data analysis for some exploratory populations will be done at sponsor discretion. Known populations of interest include [redacted]

[redacted]

10.3 General Imputation Methods

As sensitivity analyses of the primary endpoint, missing data will be imputed as failures in the study eyes which do not meet the mITT criteria at either 1 or both treatments in the pairwise treatment comparisons. A similar imputation will be done imputing missing data (data not meeting the mITT criteria) as successes in the mITT GEE analysis. Additionally, analysis on the primary efficacy variable will be performed on the ITT and PP populations using observed data only.

10.4 Primary Efficacy Variable

The primary efficacy variable in this study is the percentage of subjects who achieve a 3-line (15-letter) or greater improvement from pre-treatment in the measurement of monocular best-corrected distance VA at 45 cm at 1h post-treatment in the study eye. The comparisons between active drug (PRX-100 and [redacted] Aceclidine) versus vehicle will be considered the primary comparisons, whereas the comparison between PRX-100 and [redacted] Aceclidine will be considered a secondary comparison.

10.5 Secondary Efficacy Variables

The secondary efficacy variables are:

- The percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letter) or greater improvement from pre-treatment by 1-letter increments in the measurement of monocular best-corrected distance VA at 45 cm in the study eye for each time point
    - 0.5, 1, 3, 4, 5 and 7h post-treatment

- Percentage of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of post-treatment monocular best-corrected distance VA [redacted] compared to pre-treatment monocular best-corrected distance VA [redacted]
- Mean monocular best-corrected distance logMAR VA at near distances in the study eye
    - Post-treatment assessments compared to pre-treatment assessment
    - Two near testing distances will be assessed: [redacted] (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA at 45 cm compared to baseline binocular best-corrected distance VA at 45 cm
    - 0.5, 1, 3, 4, 5 and 7h post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular best-corrected distance VA at [redacted] compared to baseline binocular best-corrected distance VA at [redacted]
- Mean binocular best-corrected distance logMAR VA at near
    - Post-treatment assessments compared to pre-treatment assessment
    - Two near testing distances will be assessed: [redacted] (all post-treatment time points [0.5, 1, 3, 4, 5 and 7h]) and [redacted]

10.6 **Exploratory Efficacy Variables:**

The exploratory efficacy variables are:

- [redacted]

- [redacted]

10.7 Other Measures

- Measurement of pupil diameter via pupillometry under [redacted]

10.8 Sample Size

This study is expected to complete 30 evaluable subjects in each treatment group within the mITT population. Primary analyses will be evaluated at two-sided alpha levels of 0.10. The primary endpoint will have 84.7% power if [redacted] of the PRX-100 treatment subjects have at least a 3-line (15-letter) improvement from the pre-dose measurement of best distance corrected VA (monocular assessment) while the vehicle group has [redacted] with a 3-line improvement. With these same assumptions, the study will have 90.1% power to show a difference between treatments if the PRX-100 arm has [redacted] subjects with at least a 3-line improvement.

10.9 Demographic and Baseline Characteristics

Subject demographics: gender, race, ethnicity, and iris color will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics.

10.10 Primary Efficacy Analyses

The primary analyses will separately compare the PRX-100 arm versus the vehicle arm, and the [redacted] Aceclidine arm versus the vehicle arm. PRX-100 will also be compared against [redacted] Aceclidine as a secondary analysis. Only the study eye in the mITT population at the 1h post-treatment time point is considered primary.

Descriptive statistics will be presented for each time point and distance by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) improvement in the study eye from pre-dose will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by generalized estimating equation methods. Aspects of the model include:

- Response measure: indicator of whether the subject had at least a 3-line (15-letter) improvement in the study eye from pre-dose in the monocular assessment of best-corrected distance VA at [redacted].

- Fixed effect explanatory measures: sequence, period, and treatment.

- Random effect measure: subject within sequence, to account for the correlation between treatments and periods within a subject.

- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix.

Standard errors and CIs (80 and 90%) will also be presented for each treatment group and the difference between treatment groups. Separate models will be built for each distance (with 45 cm being primary and [redacted] being secondary) and time point separately. Pairwise comparisons among treatment groups will also be made at each distance and time point using McNemar's tests.

10.11 Secondary Efficacy Analysis

Descriptive statistics will be presented for each time point and distance as well as for the change from pre-dose at each time point and distance by treatment group. The same logistic regression models developed for the primary analyses will be used to test secondary proportion endpoints. For continuous secondary endpoints, similar mixed effect models will be employed. Two-sided one-sample *t*-tests from a mixed effects linear model with monocular best-corrected distance VA at near from pre-dose as the response variable; sequence, period, and treatment as fixed effect variables; and subject within sequence as a random effect term with a variance component covariance matrix to account for the correlation among measures within a subject using $\alpha = 0.10$ and two-sided 80% and 90% CI will be provided as additional descriptors of the data. Separate models will be built for each distance and time point separately. Pairwise comparisons among treatment groups will also be made at each distance and time point using one-sample *t*-tests.

10.12 Exploratory Efficacy Analysis

Exploratory efficacy endpoints will be analyzed for all available data similarly to the primary and secondary endpoints in the mITT population and in the ITT population for sensitivity. All exploratory variables will include percentage based

and mean based analyses, similar to the primary and secondary endpoints. Pairwise treatment comparisons will be calculated where possible, along with changes from pre-treatment; otherwise, analyses will be limited to within treatment statistics.

Exploratory efficacy analysis will occur in the three dynamic definitions of the study eye based on baseline BCVA at 45 cm, pupil size, [redacted] and in subgroups of interest to the Sponsor.

10.13 Other Measures

Pupil diameter will be analyzed using similar statistical methods to that of the secondary efficacy variable of best-corrected distance VA [redacted]

10.14 Adjustment for Multiplicity

There will be no adjustments for multiplicity in testing the primary efficacy endpoint at each time point at a distance of [redacted] in this proof of concept study. There will be no adjustments for multiplicity for multiple treatment arms and multiple comparisons to vehicle either.

10.15 Safety Analysis

The percentage of subjects with treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Slit lamp biomicroscopy, IOP, conjunctival redness, best-corrected VA, low-luminance best-corrected VA will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to

enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Ora and/or study sponsor and provided in writing by Ora and/or study sponsor prior to the consent process.

11.1.2 IRB Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/ERC approved version of the ICF will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms (EKGs). The Investigator's copy of the eCRFs serves as the Investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all investigational products and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits, following the randomization list generated prior to the start of the study. Each clinical kit will be uniquely identified by the 4-digit subject number and visit number listed on the kit.

Clinical label texts for the primary packaging (glass vials) and secondary packaging (clinical kits) meet applicable regulatory requirements and include the statement "Caution: New Drug-Limited by Federal Law to Investigational Use."

11.5.2 Storage of Investigational Product

Investigational drug must be stored in a secure area of the investigative site, accessible only to Investigator or designees, at room temperature between 15° - 25°C (59-77°F). The investigational product will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. All investigational drugs will be returned to inventory after use.

11.5.3 Accountability of Investigational Product

The investigational product is to only be administered by the principal Investigator or his/her named sub Investigator(s), and is to only be used in accordance with this protocol. The investigational product must only be distributed to subjects properly qualified under this protocol to receive investigational product.

The Investigator must keep an accurate accounting of the investigational product received from the supplier. This includes the amount of investigational product administered to subjects and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the investigational product.

11.5.4 Return or Disposal of Investigational Product

All investigational products will be returned to the sponsor or their designee or destroyed. The return or disposal of investigational product will be specified in writing.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's source document, eCRF and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

11.7 Handling of Biological Specimens

Not applicable

11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the study sponsor will have the final decision regarding the manuscript and publication.

12 REFERENCES

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Appendix 1: Schedule of Visits and Measurements

Study Parameter	Visit 1 (Day 1)	Visit 2 (Day 15 ± 7)	Visit 3 (Day 29 ± 7)	Visit 4 (Day 43 ± 7)
Informed consent / HIPAA	X			
Demographic data	X			
Medical and medication history	X			
Medical and medication history update		X	X	X
Urine pregnancy test (for females of child-bearing potential)	X	X	X	X
Inclusion and exclusion criteria review	X			
Baseline pupillometry [redacted]		X	X	X
Screening monocular best-corrected distance visual acuity at [redacted][1]	X			
Baseline monocular best-corrected distance visual acuity at [redacted]		X	X	X
Baseline binocular best-corrected distance visual acuity at [redacted]		X	X	X
Baseline monocular best-corrected distance visual acuity at [redacted]		X	X	X
Baseline binocular best-corrected distance visual acuity at [redacted]		X	X	X
Screening monocular best-corrected distance visual acuity[1]	X			
Baseline monocular best-corrected distance visual acuity[1]		X	X	X
Baseline binocular best-corrected distance visual acuity[1]		X	X	X
Baseline monocular low-luminance best-corrected distance visual acuity[1]		X	X	X
Baseline binocular low-luminance best-corrected distance visual acuity[1]		X	X	X
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]		X	X	X
Slit lamp biomicroscopy	X	X	X	X
Baseline conjunctival redness assessment		X	X	X
Randomization		X		
Fluorescein staining[2]	X			
[redacted]				
[redacted]				
[redacted]	X			
Instillation of PRX-100, aceclidine or vehicle treatment OU[4]		X	X	X
Adverse event query (post-treatment and 1 hour post-treatment)[3]		X	X	X
Post-treatment conjunctival redness assessment (0.5, 1, 3, 4, 5, 7 hours post-treatment)[3]		X	X	X
Post-treatment pupillometry under [redacted]		X	X	X
Post-treatment monocular best-corrected distance visual acuity at 45 cm (0.5, 1, 3, 4, 5, 7 hours post-treatment)[1, 3]		X	X	X
Post-treatment binocular best-corrected distance visual acuity at 45 cm (0.5, 1, 3, 4, 5, 7 hours post-treatment)[1, 3]		X	X	X
Post-treatment monocular best-corrected distance visual acuity at [redacted]		X	X	X
Post-treatment binocular best-corrected distance visual acuity at [redacted]		X	X	X

Study Parameter	Visit 1 (Day 1)	Visit 2 (Day 15 ± 7)	Visit 3 (Day 29 ± 7)	Visit 4 (Day 43 ± 7)
Post-treatment monocular best-corrected distance visual acuity (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment binocular best-corrected distance visual acuity (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment monocular low-luminance best-corrected distance visual acuity (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment binocular low-luminance best-corrected distance visual acuity (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
End of visit slit lamp biomicroscopy	X	X	X	X
IOP	X	X	X	X
Adverse event query	X	X	X	X
Selection of study eye	X			
Assessment for study exit	X	X	X	X
Study exit	X[5]	X[5]	X[5]	X[5]

1. Visual acuity to be assessed with best distance-correction [redacted]
2. Subject should wait at least 30 minutes with his/her eyes closed following fluorescein staining prior to instillation of placebo.
3. Best effort will be made to adhere to post-placebo/post-treatment assessment time points. No minimum/maximum windows are defined for any post-placebo/post-treatment assessment time point.
4. [redacted]
5. Study exit can occur at either visit 1, 2, 3 or 4. If subject completes the study, Study Exit will occur at Visit 4.

Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

Urine Pregnancy Test

Female subjects of childbearing potential will have a urine pregnancy test at the site on the day of study visit 1, 2, 3, and 4. Pregnancy tests (Clarity HCG urine test strips, RAC Medical Boca Raton, FL) will be used.

Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed at study visit 1, 2, 3 and 4. The Investigator will note any findings present and whether or not the findings are clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the Investigator) or not clinically significant (NCS). Findings which are clinically significant will be described. All findings will be documented on each subject's source document and corresponding eCRF.

The following will be examined at each visit:

- Eyelid
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Lens

Slit-lamp biomicroscopy will be performed using a slit lamp. Magnification will be consistent with the Investigator's standard clinical practice. The subject will be seated for the examination.

[redacted]

each letter, line-by-line, left to right. The examiner should remind subjects that they are not

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
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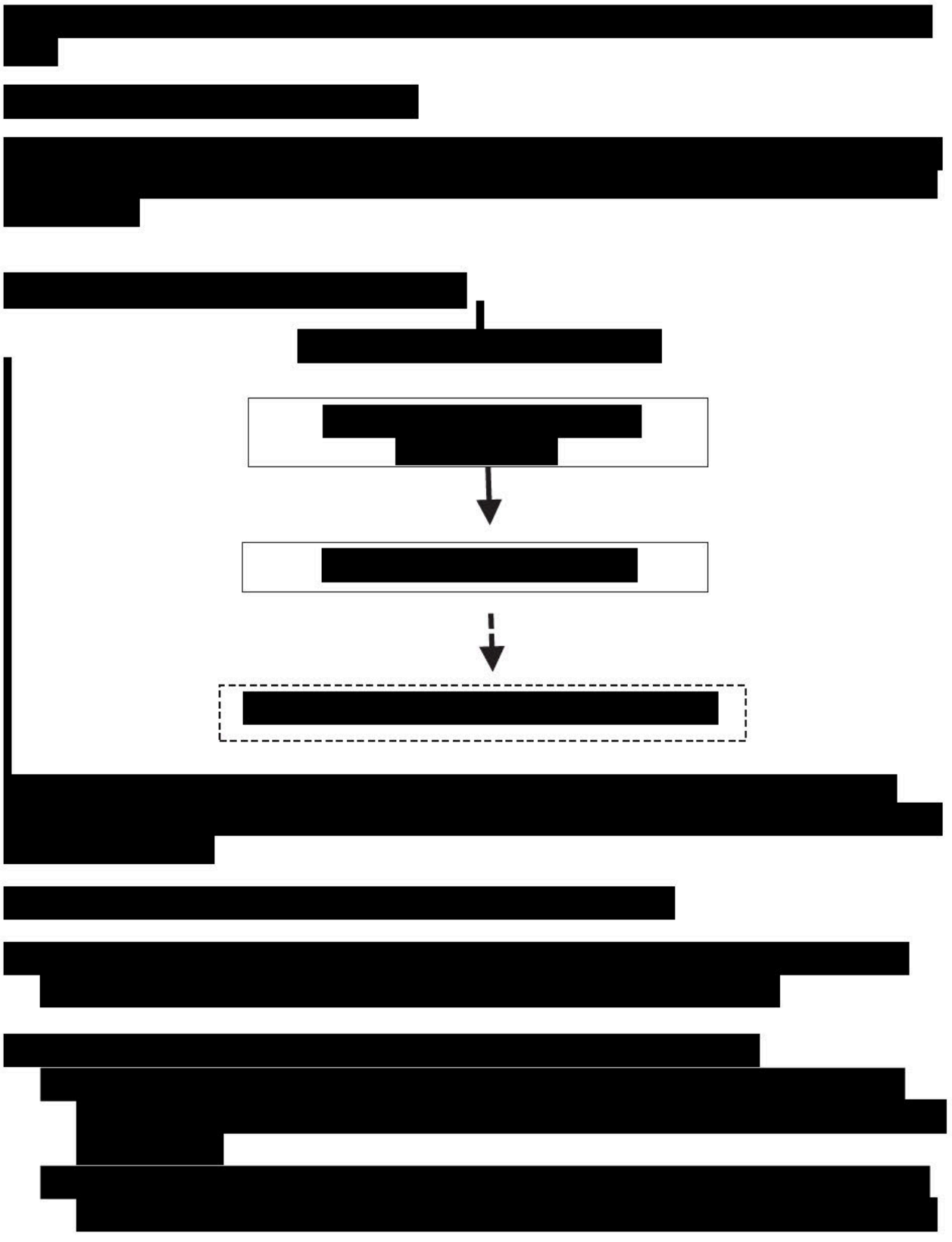

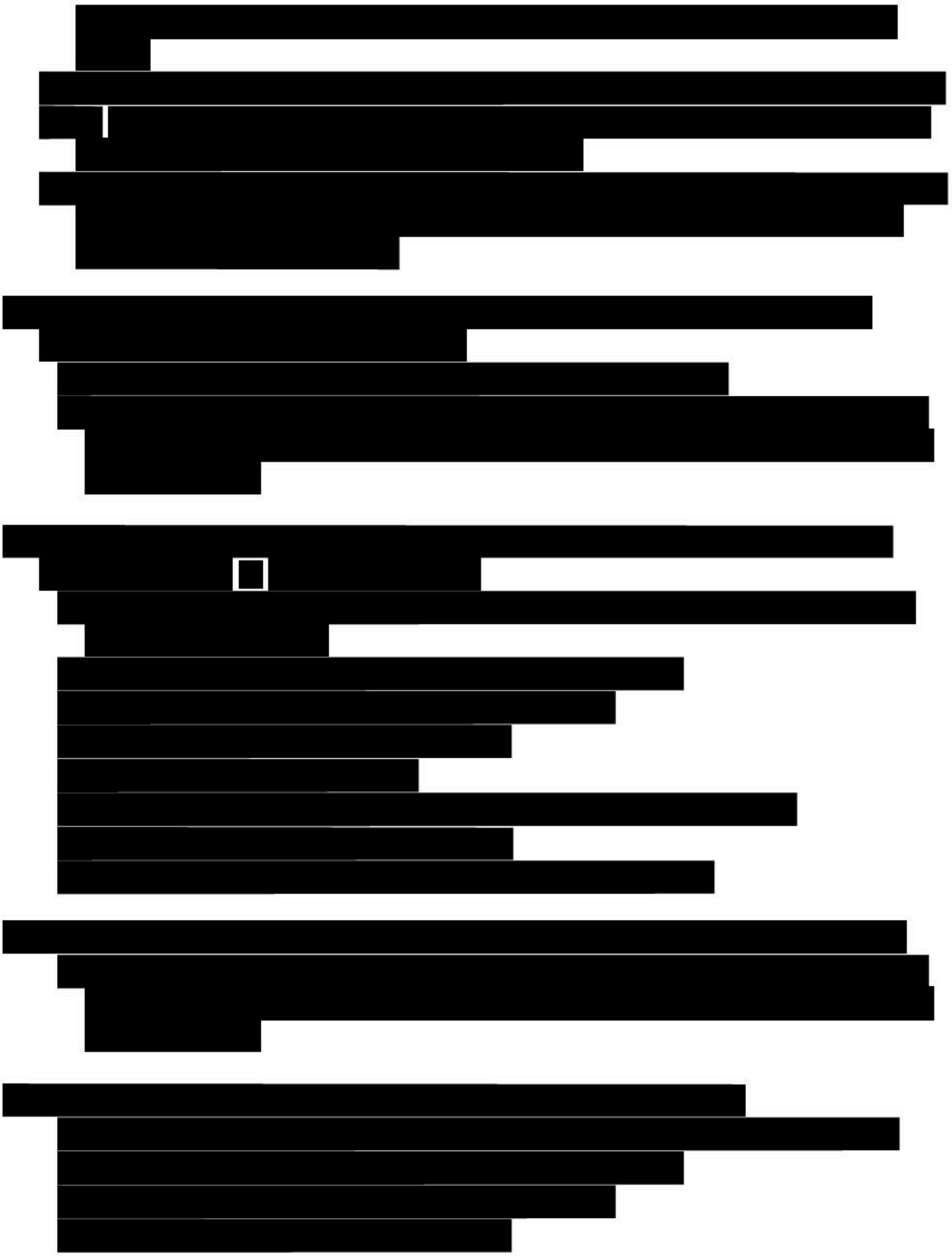

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Intraocular Pressure

[redacted]

Appendix 3: Handling of Biological Specimens

Not applicable

Appendix 4: Protocol Amendment Summary

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
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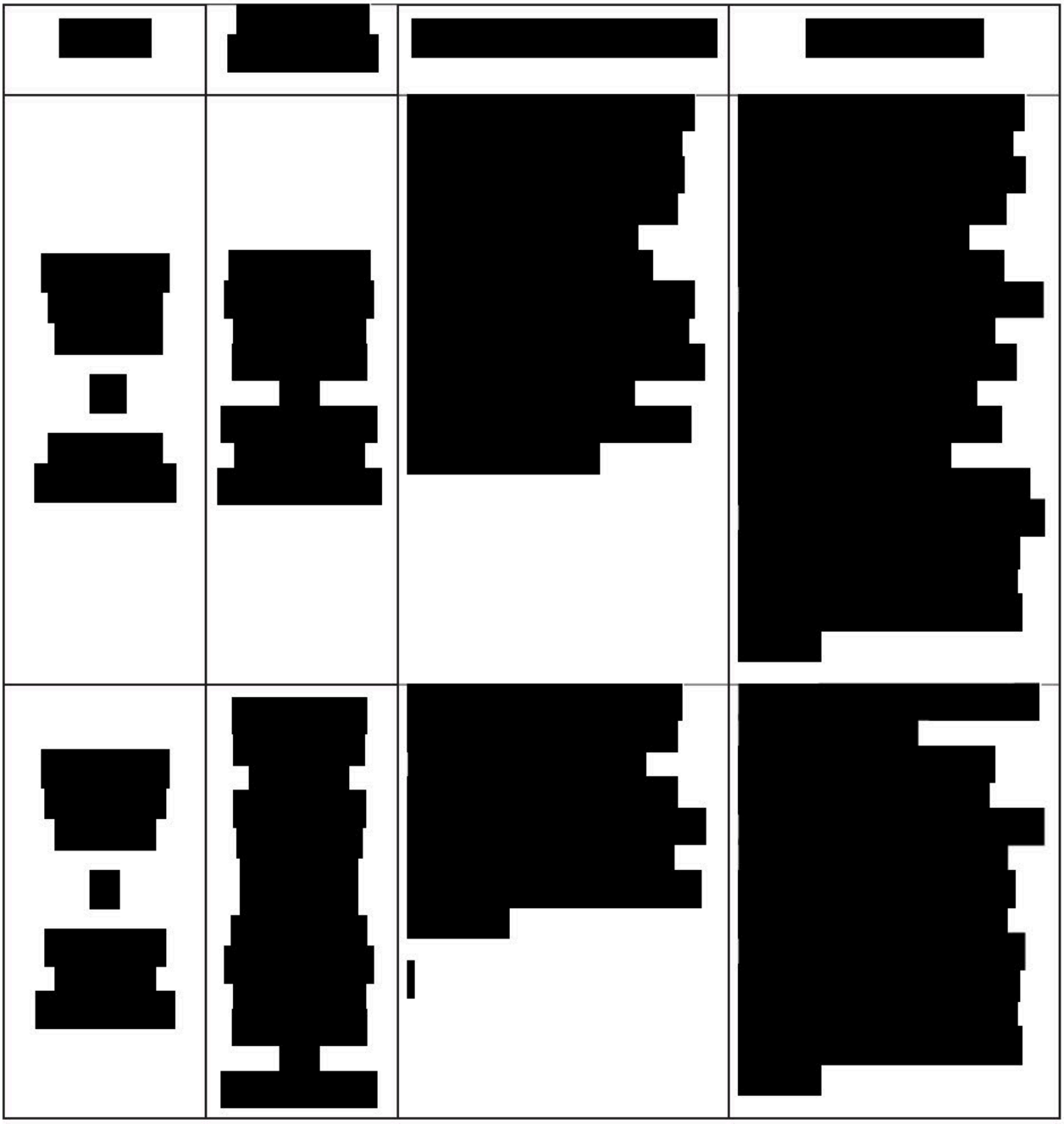

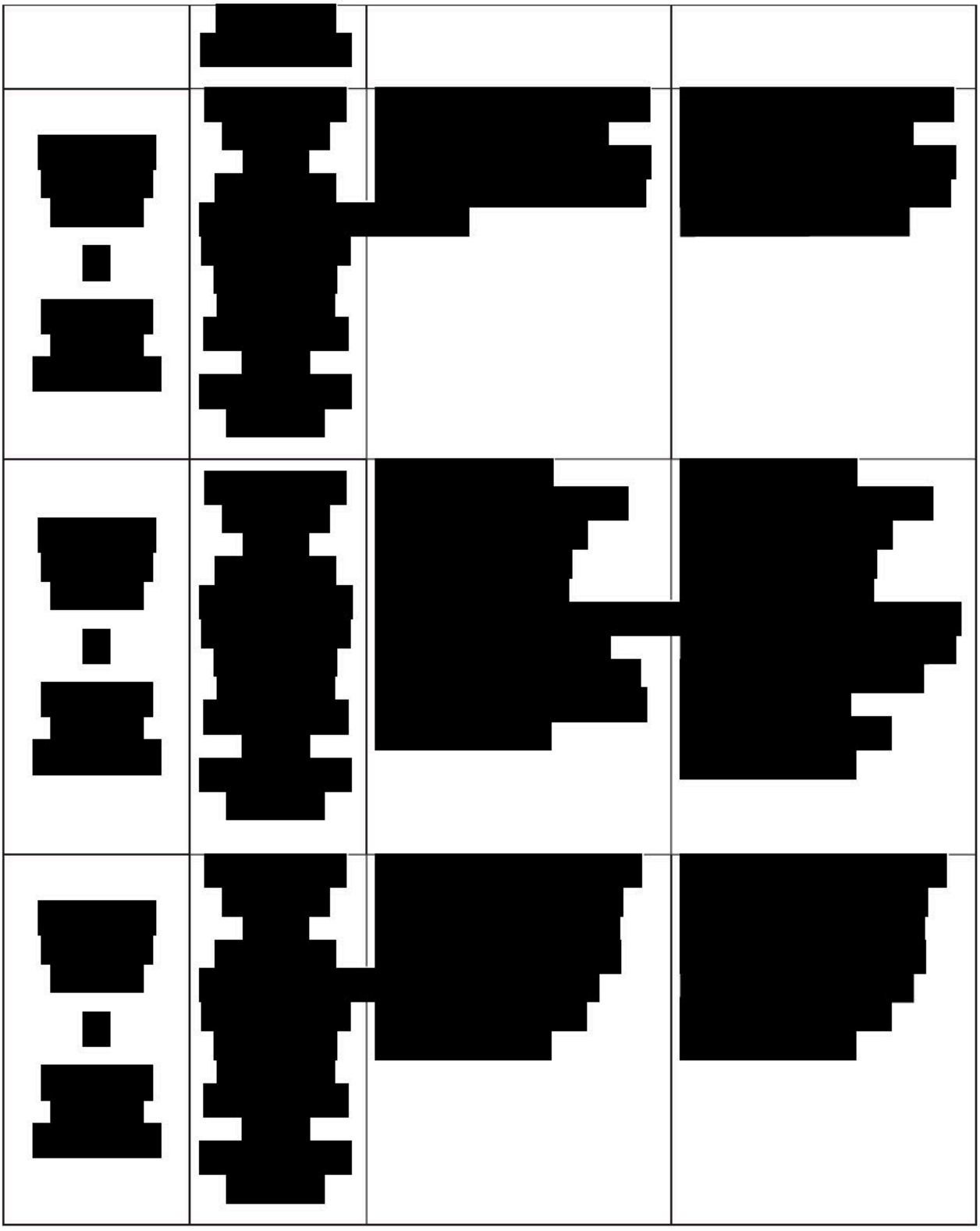

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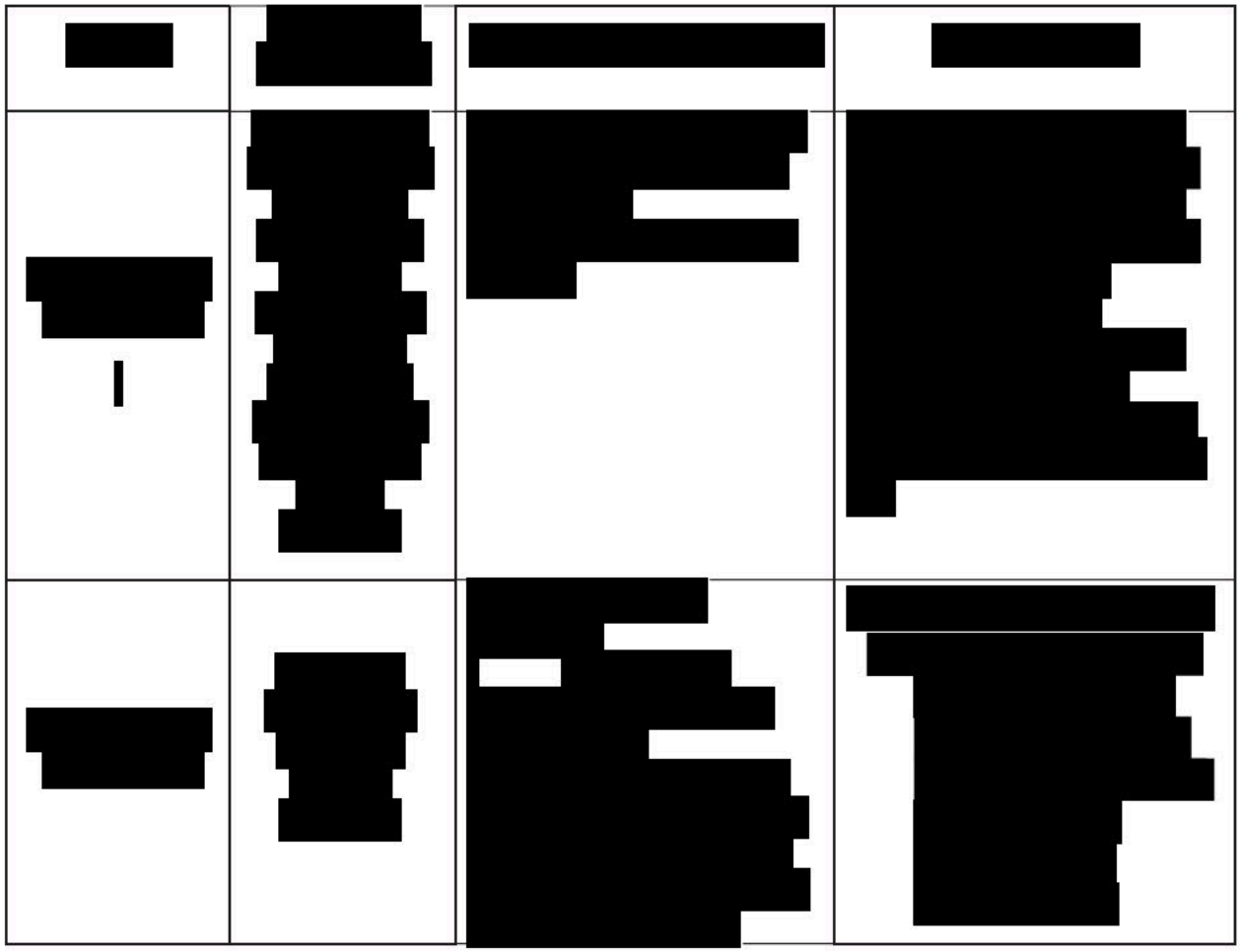

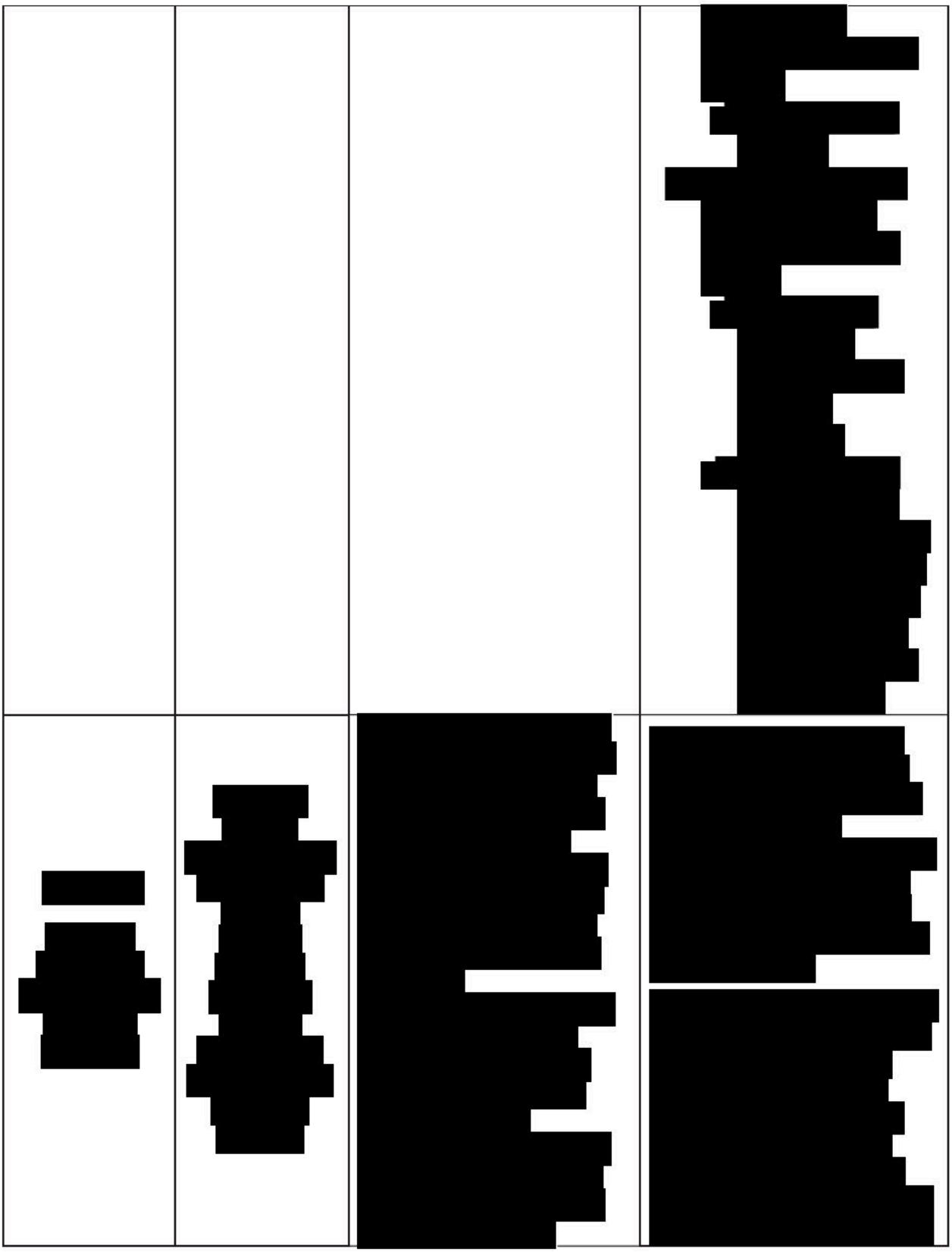

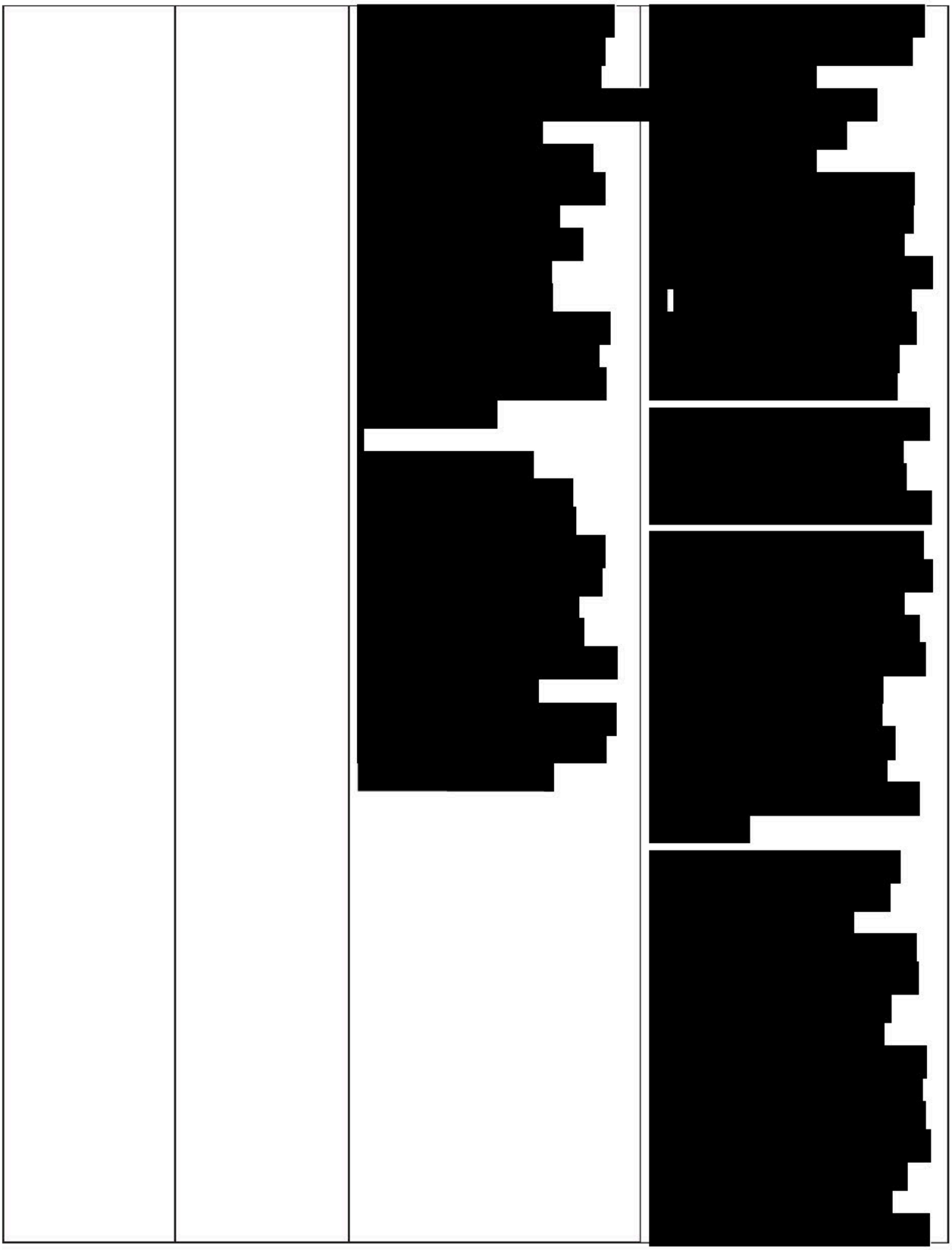

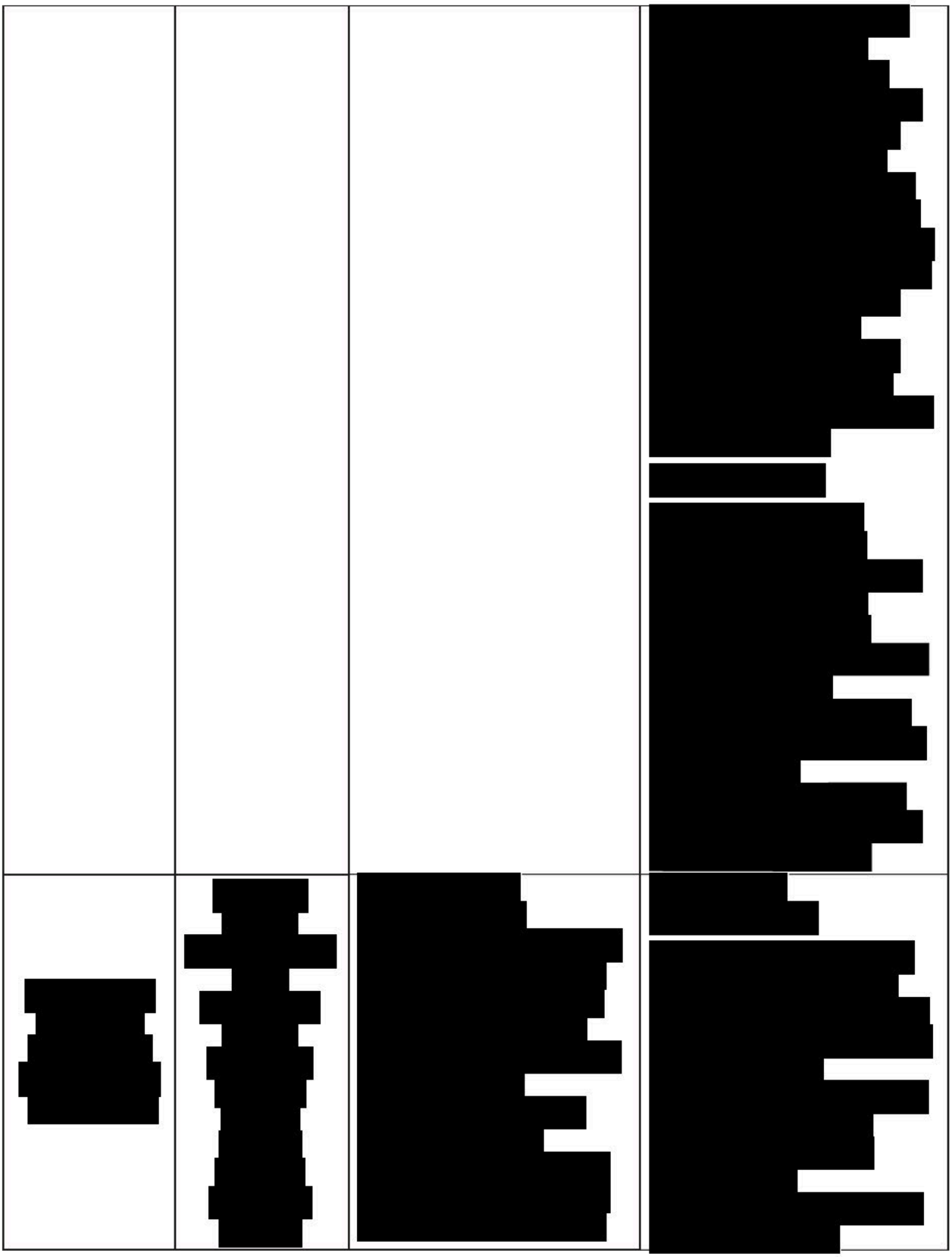

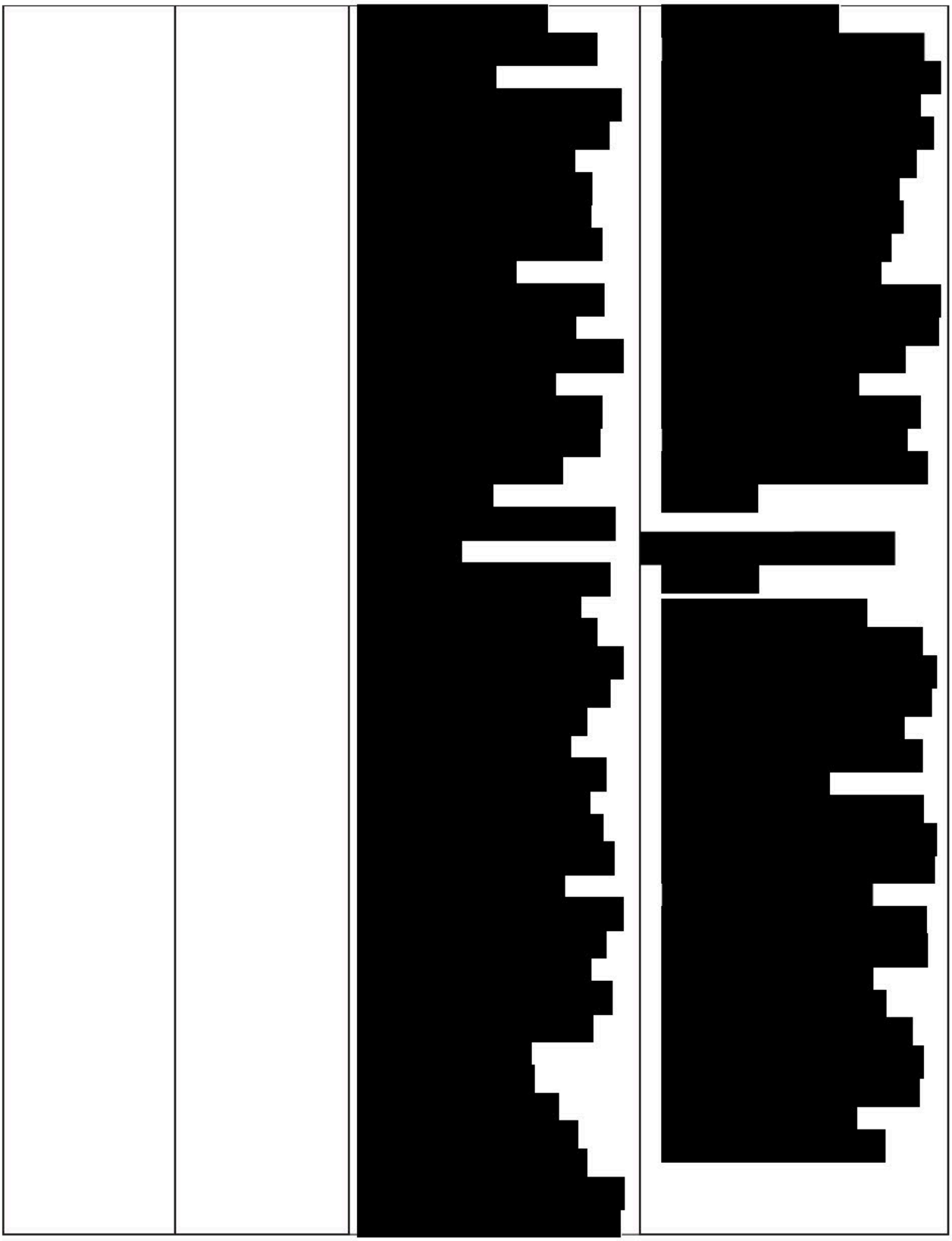

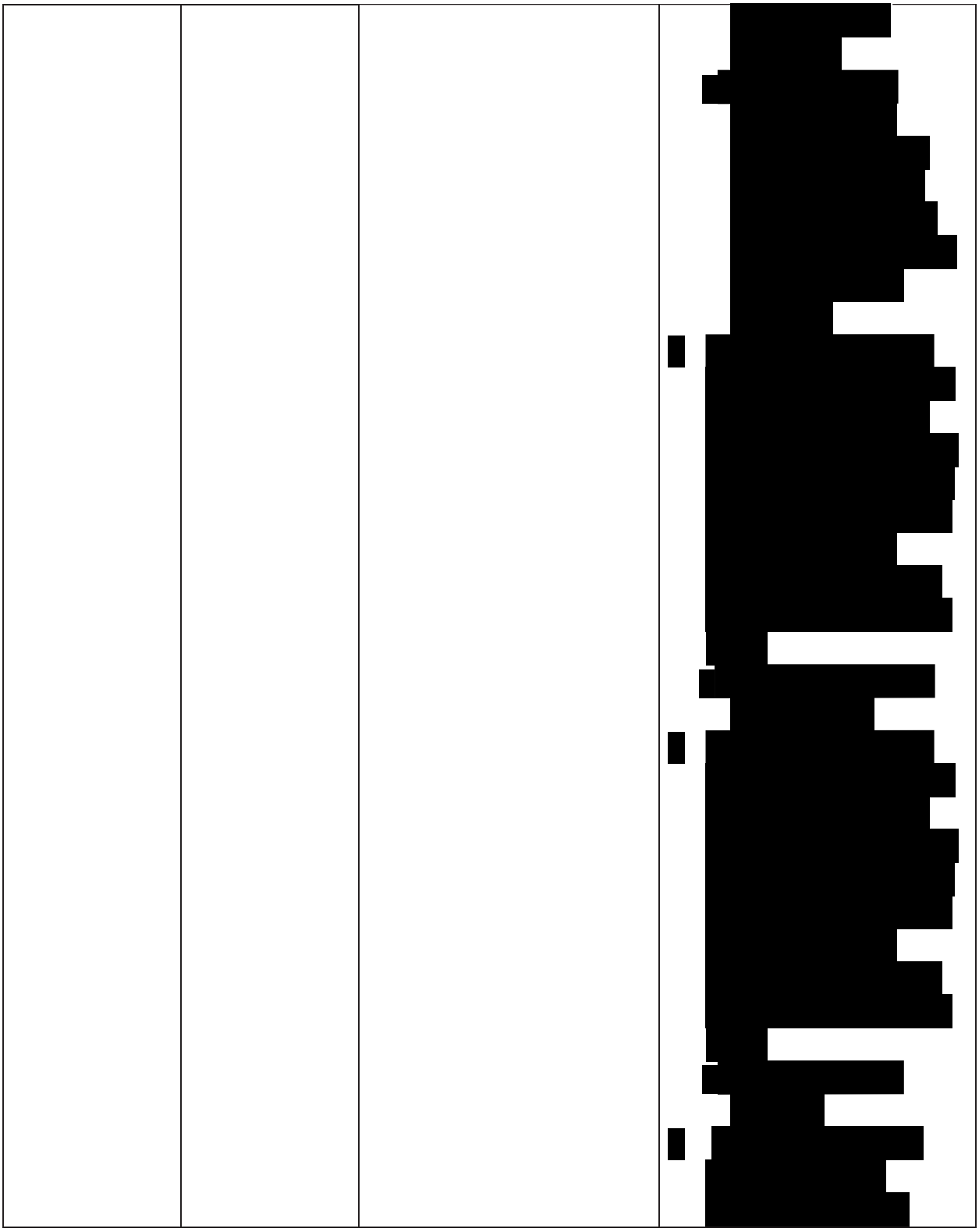

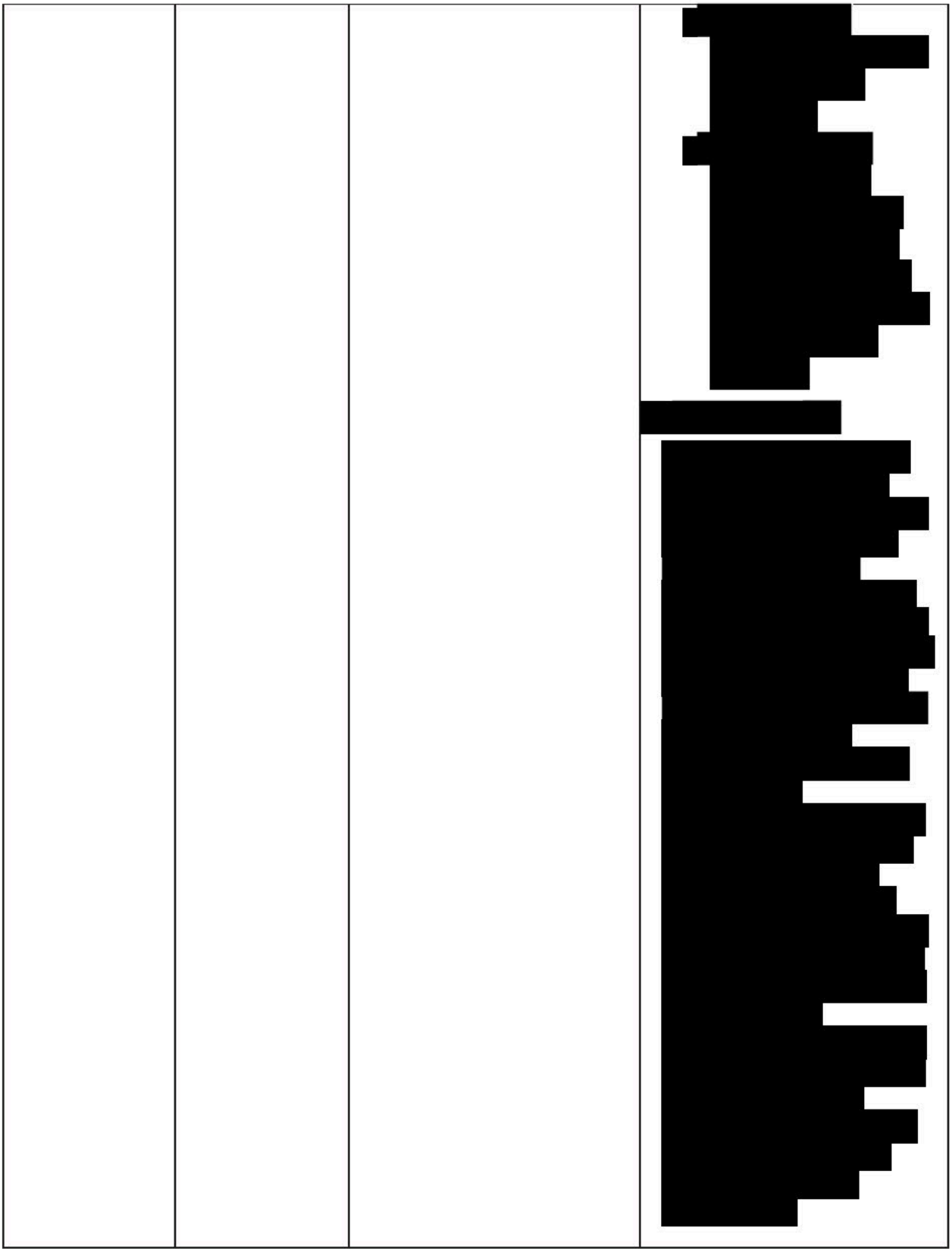

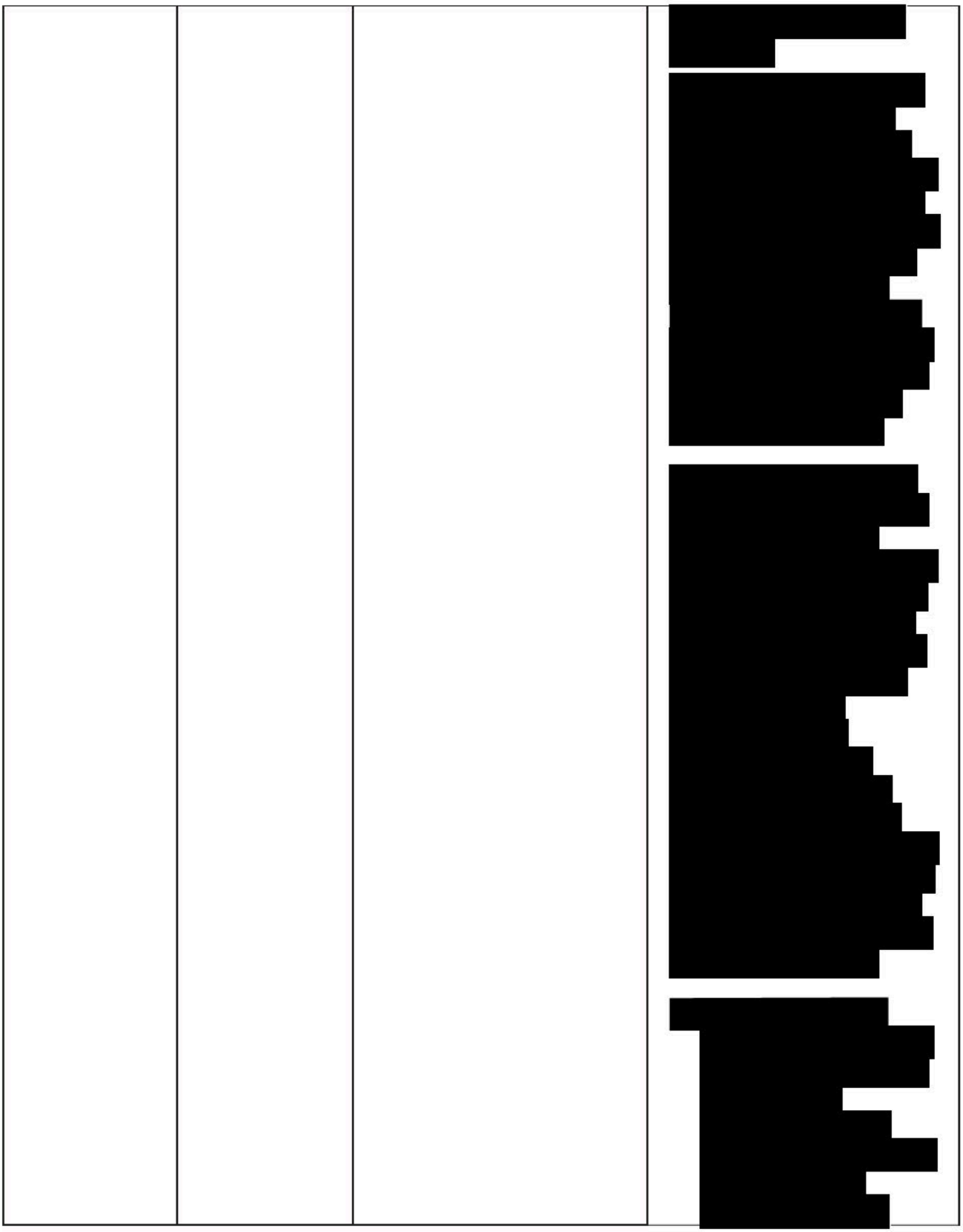

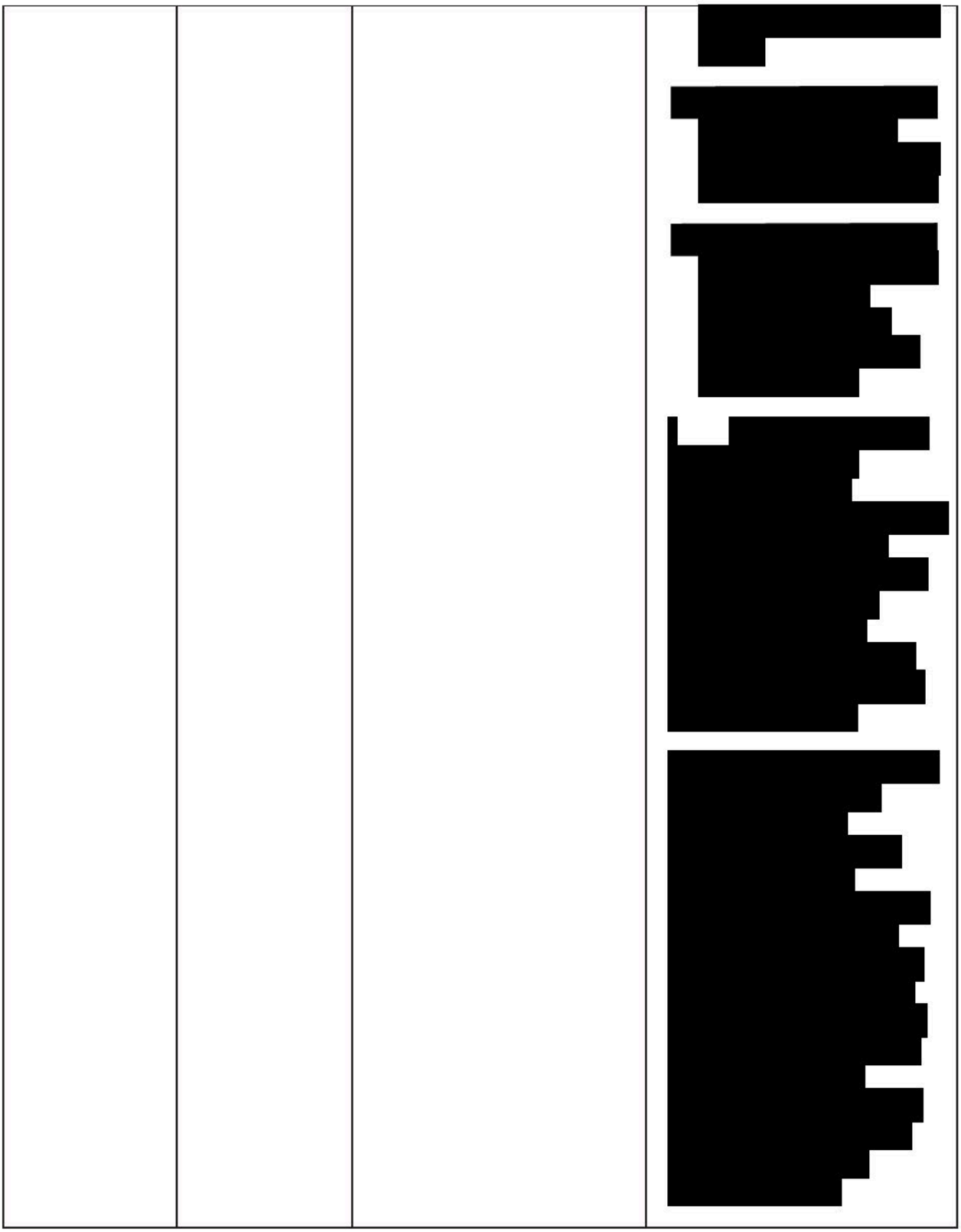

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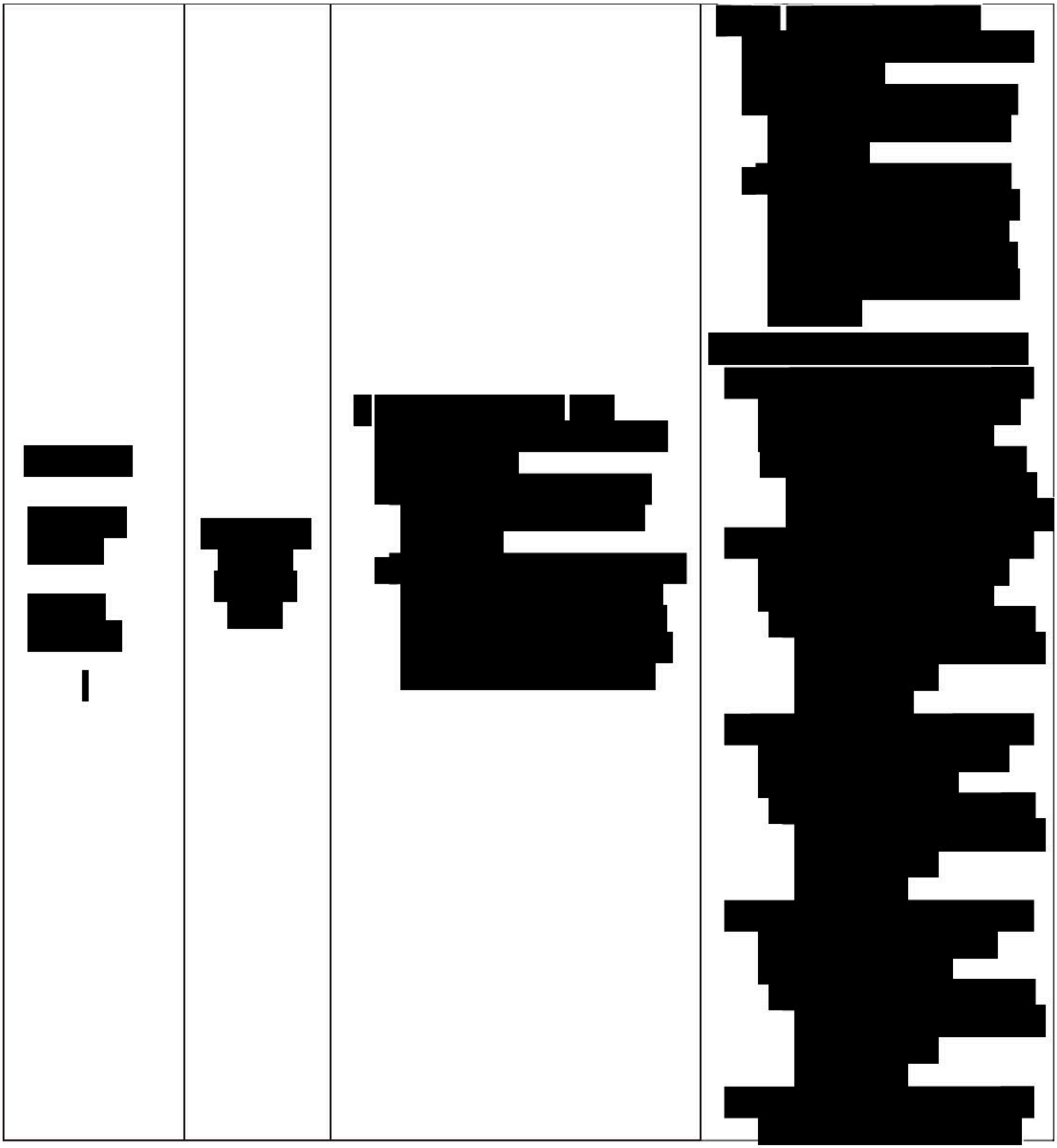

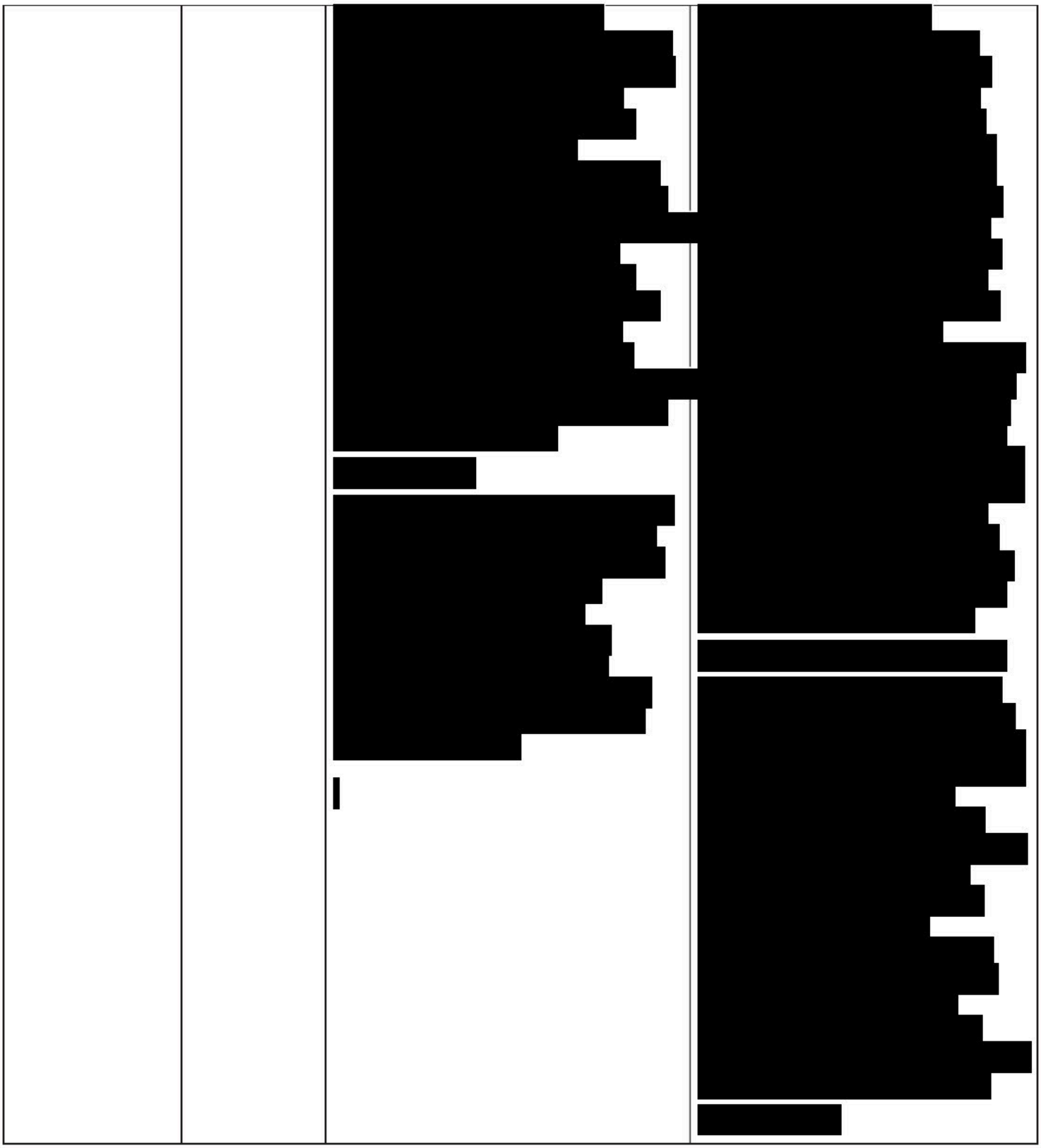

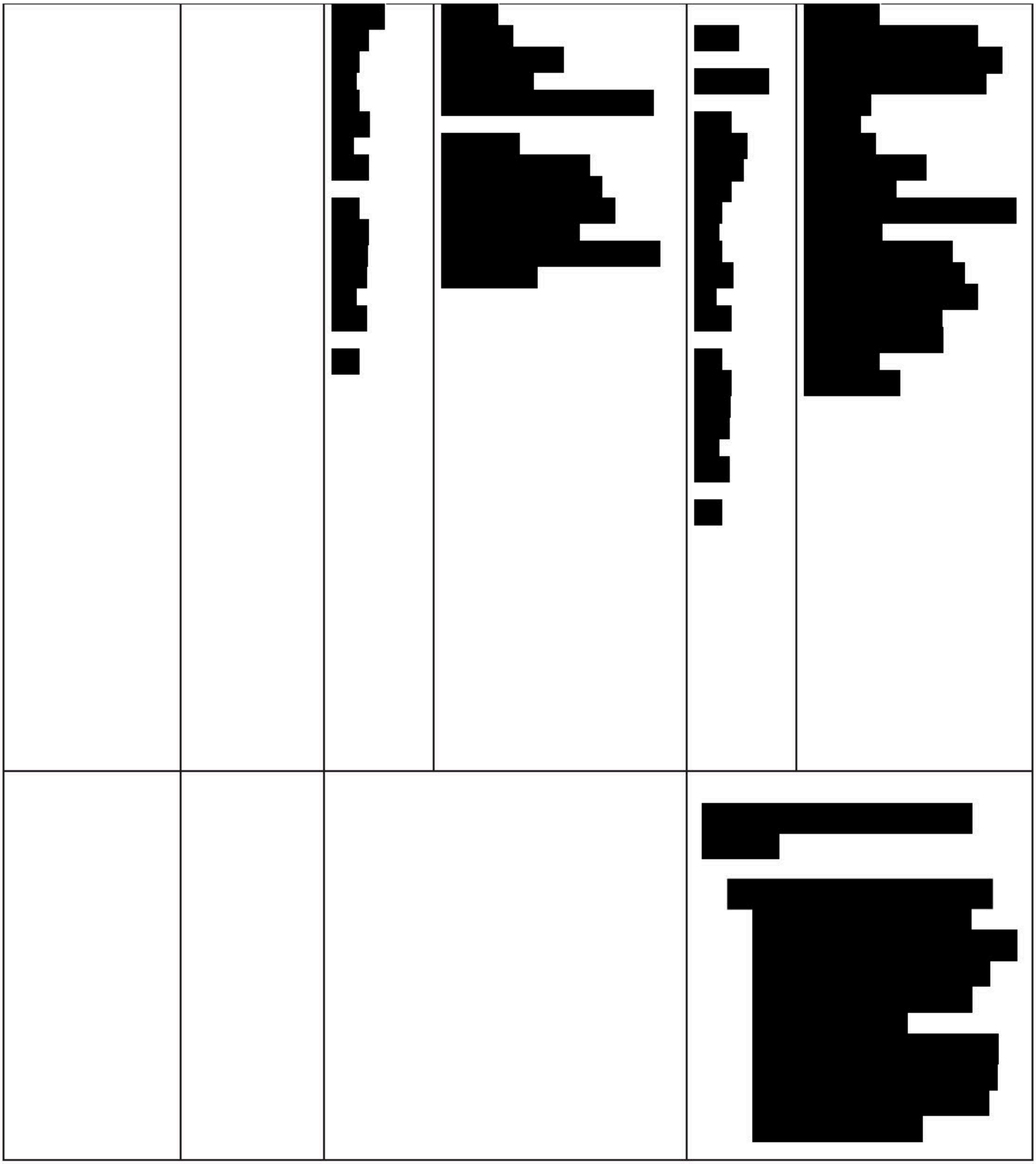

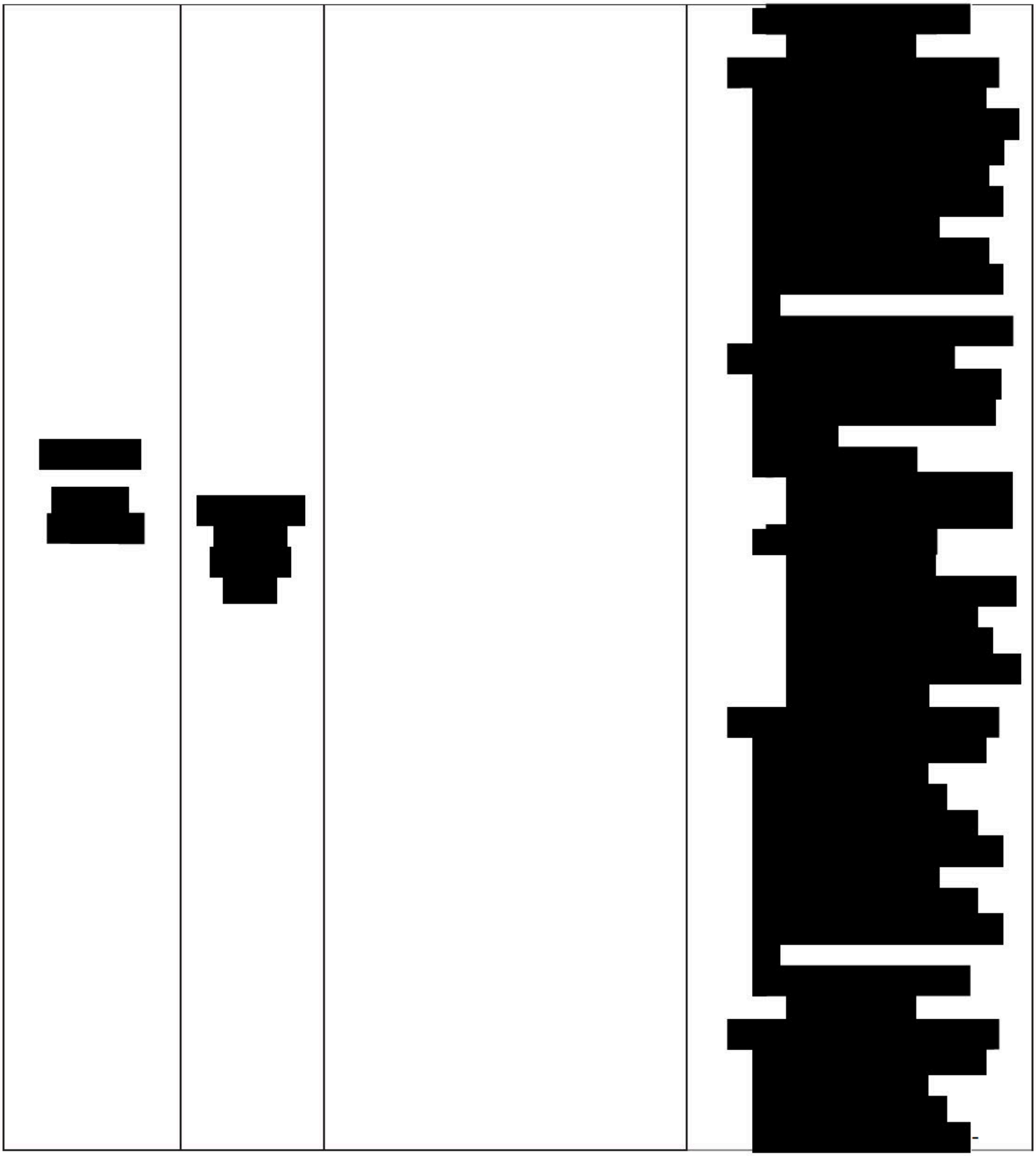

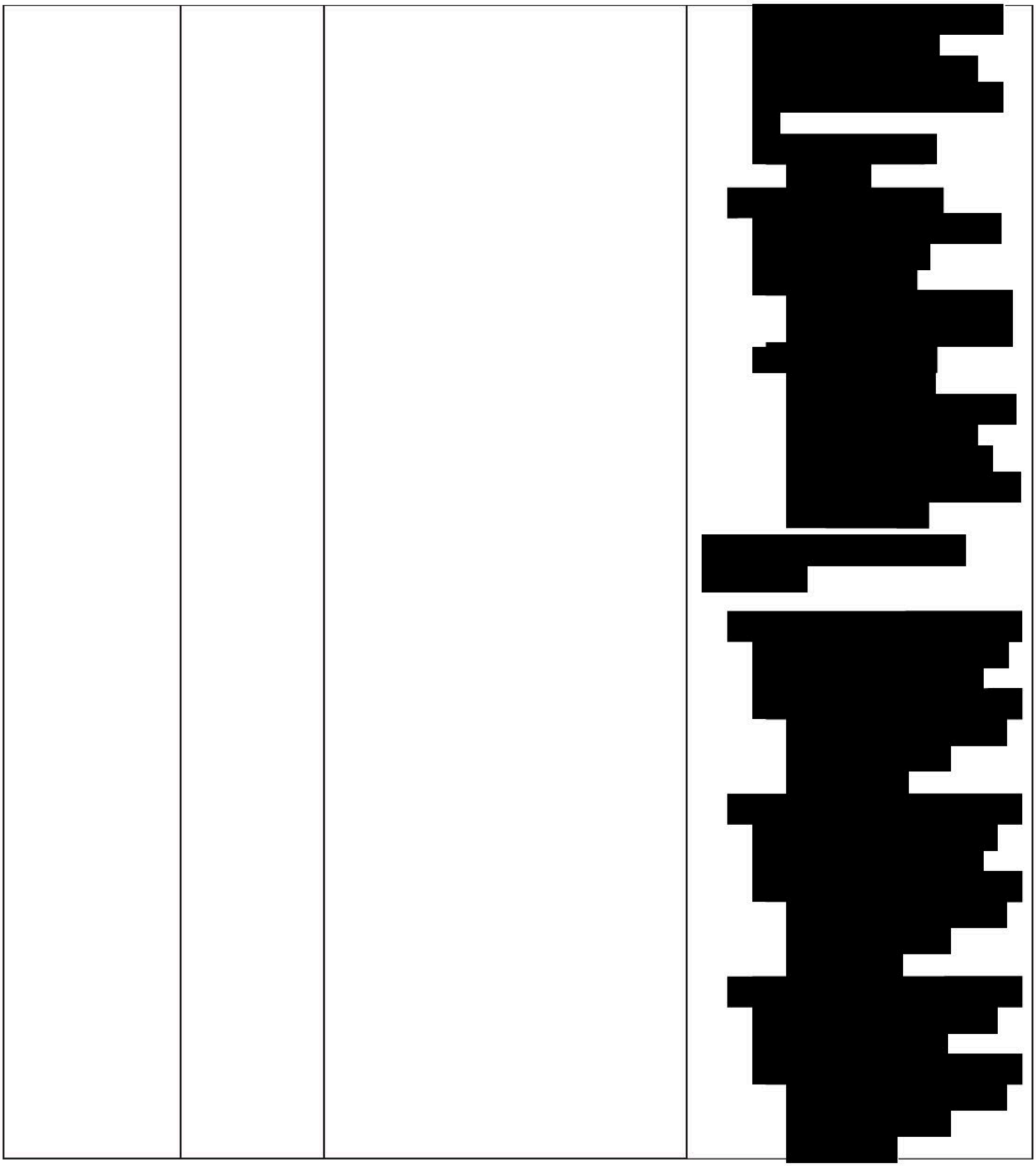

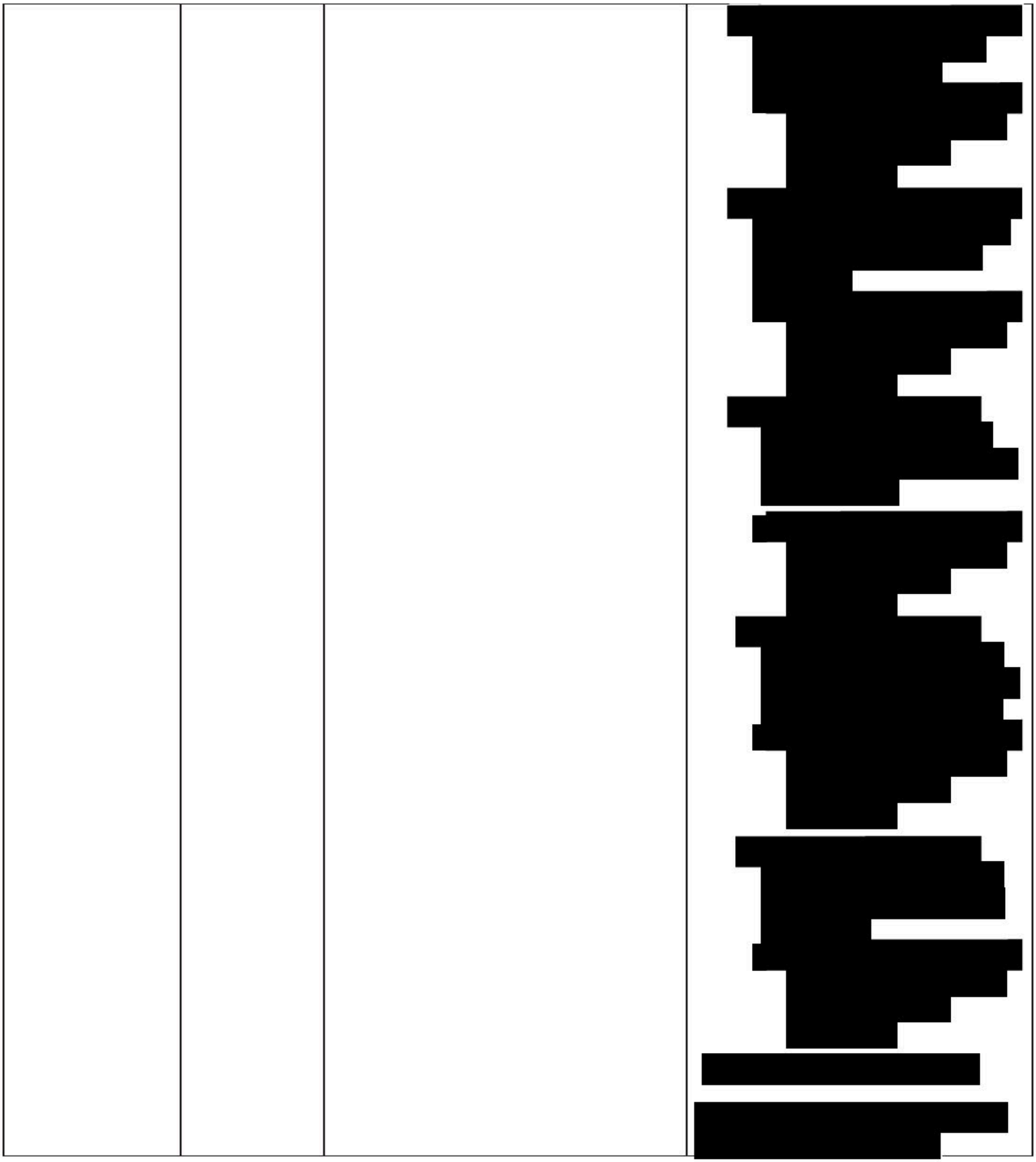

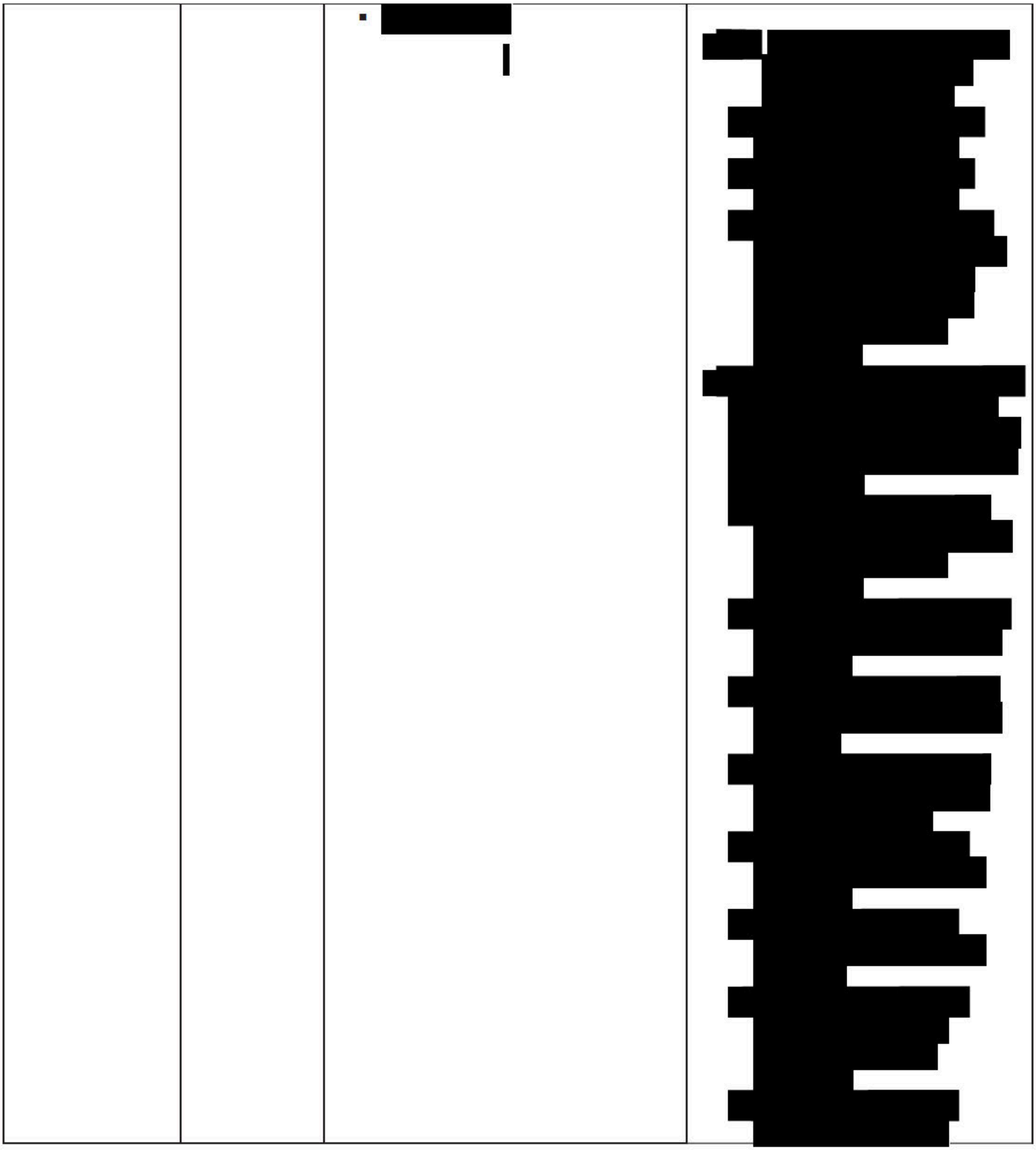

			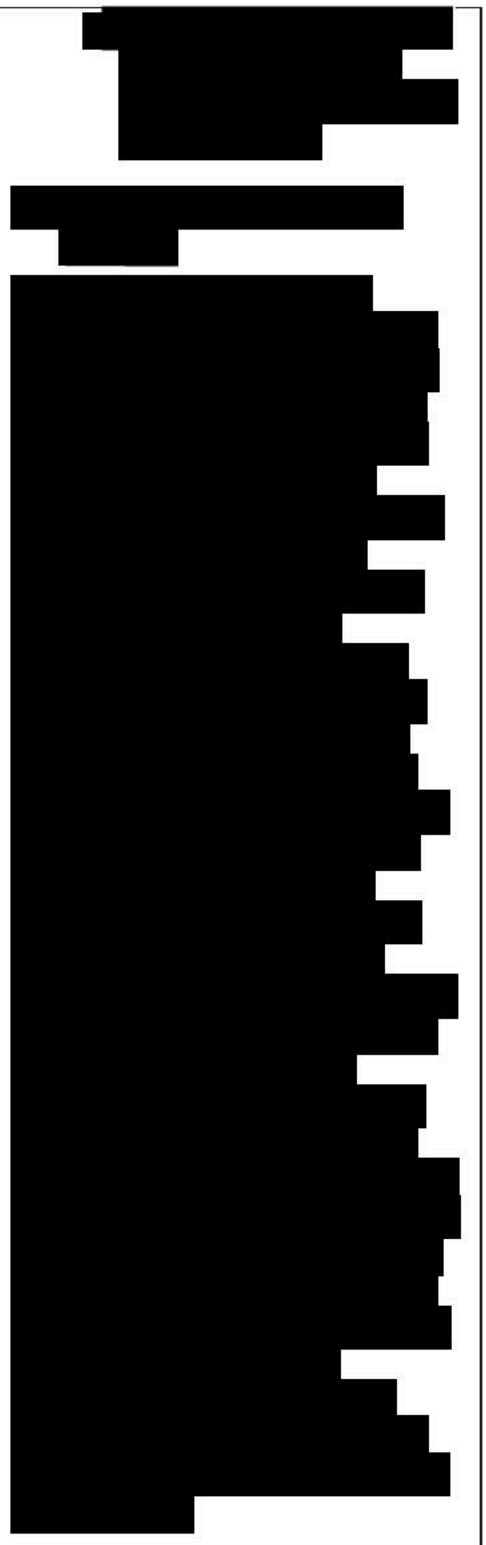

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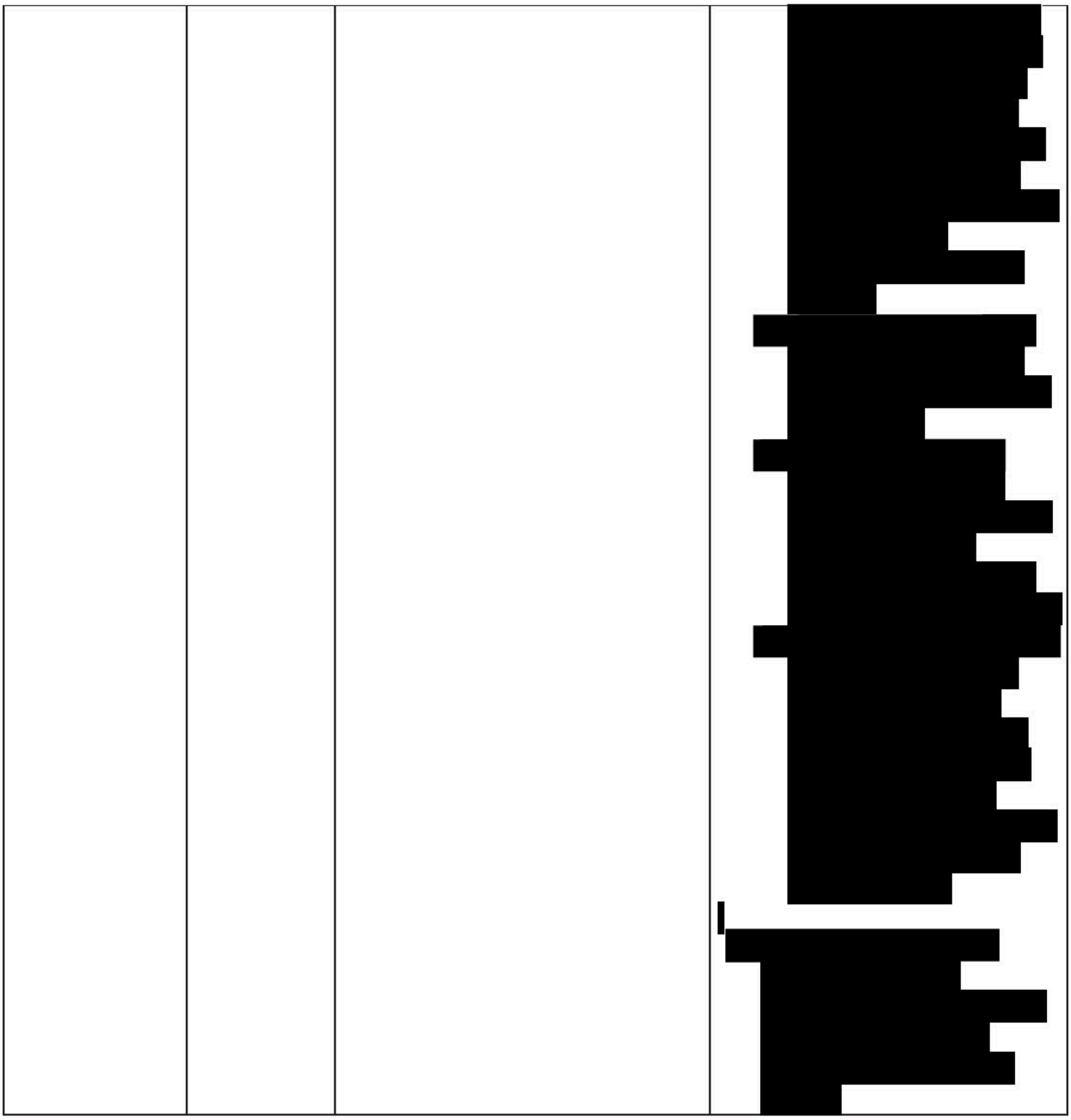

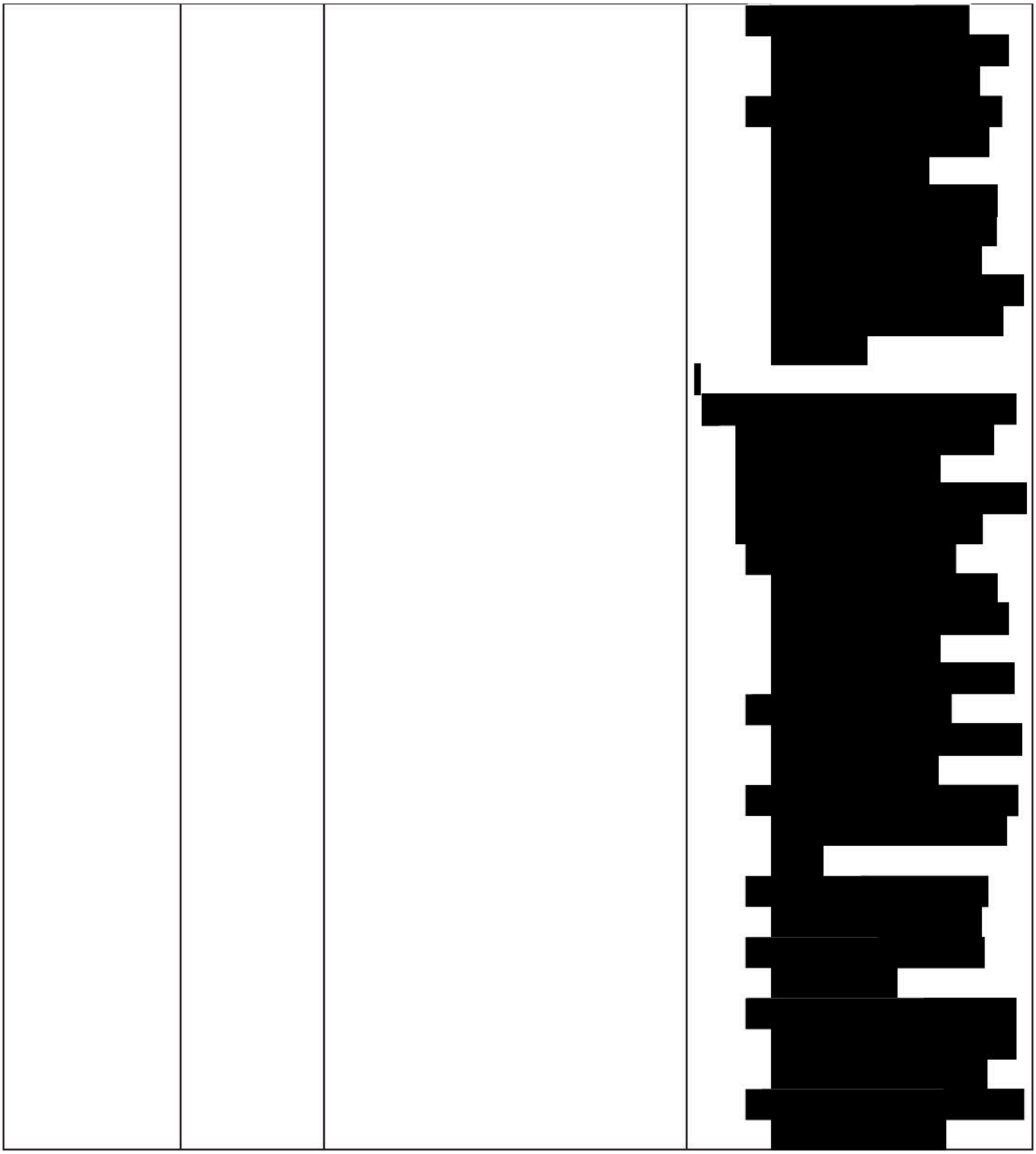

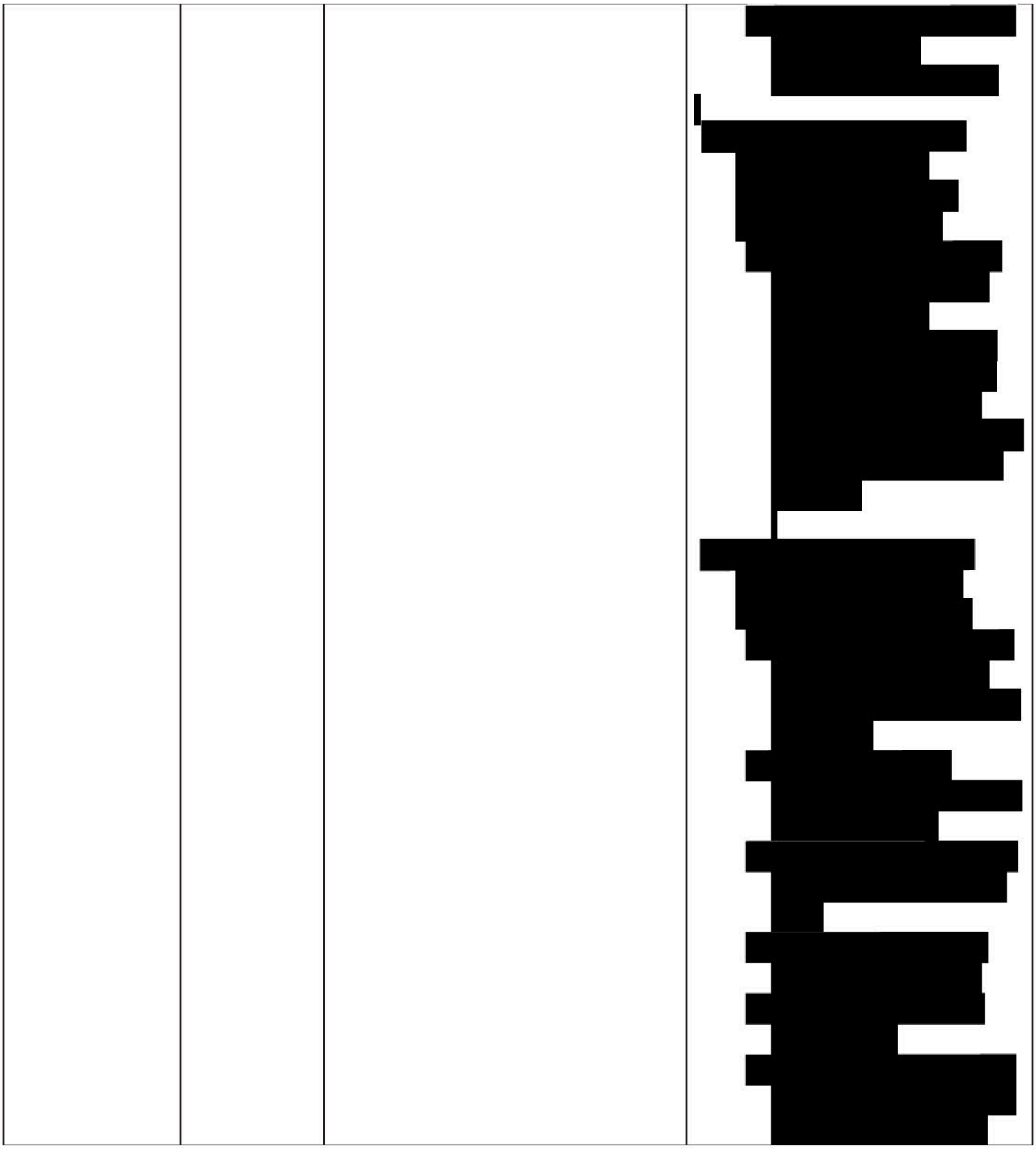

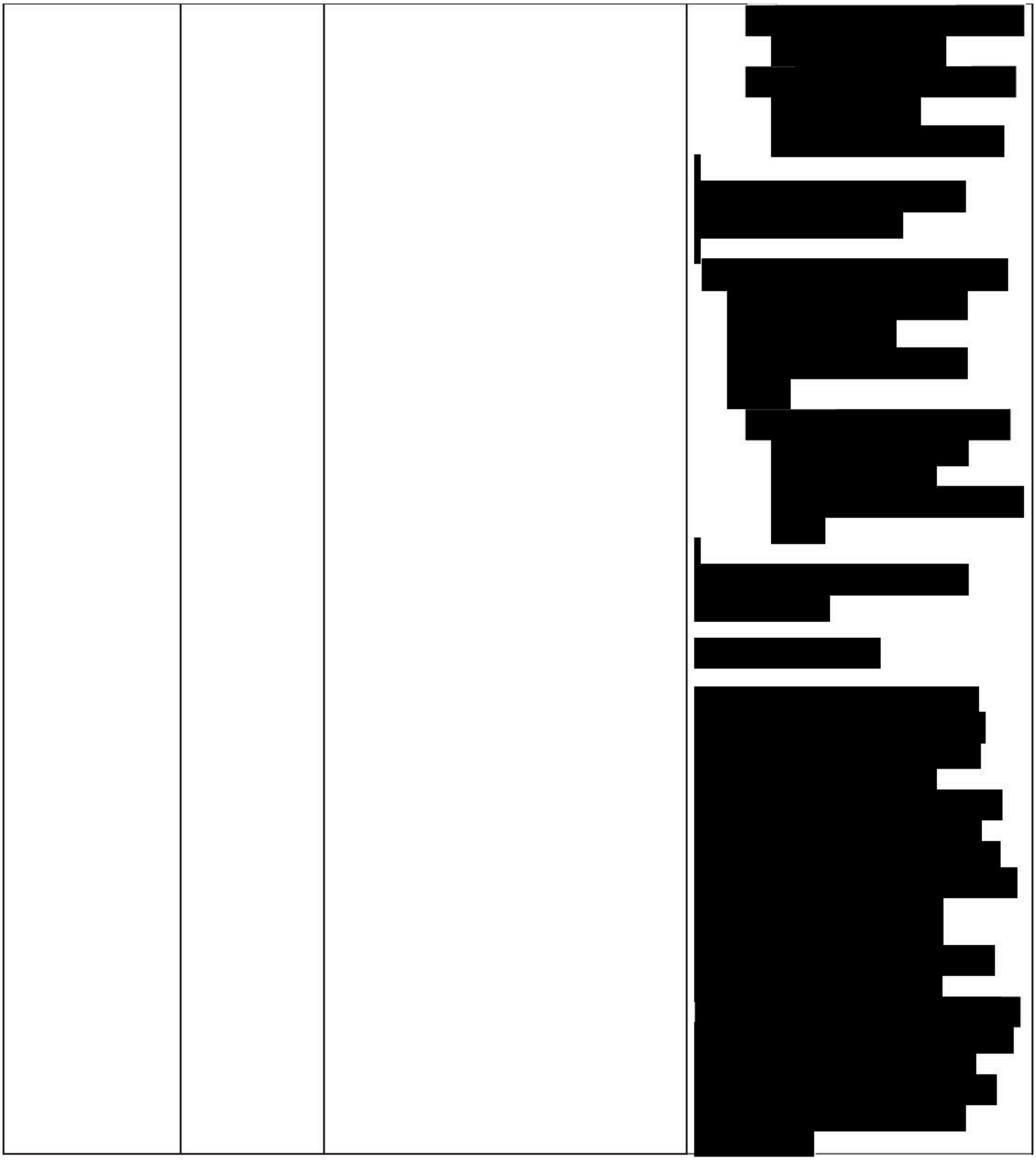

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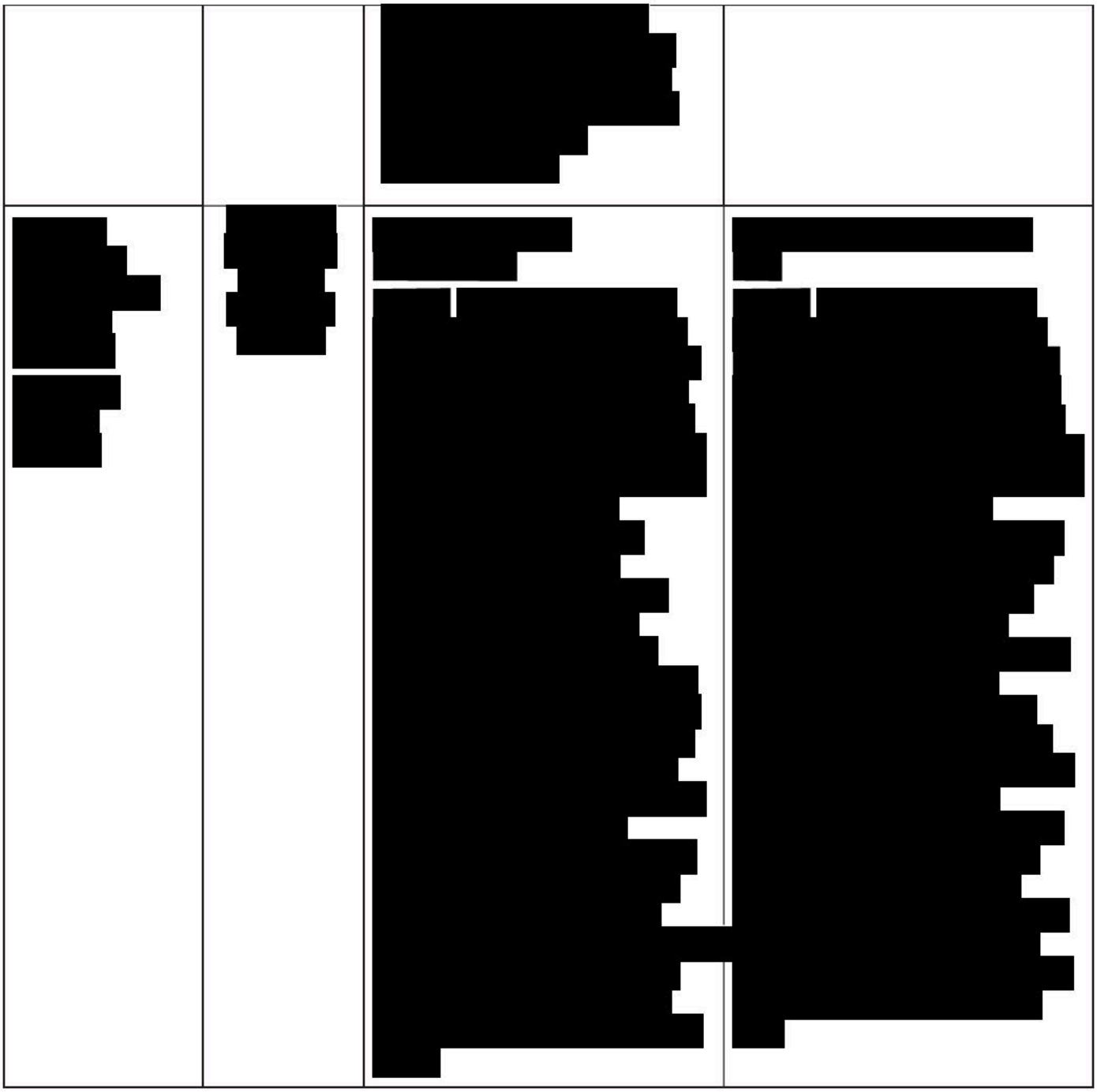

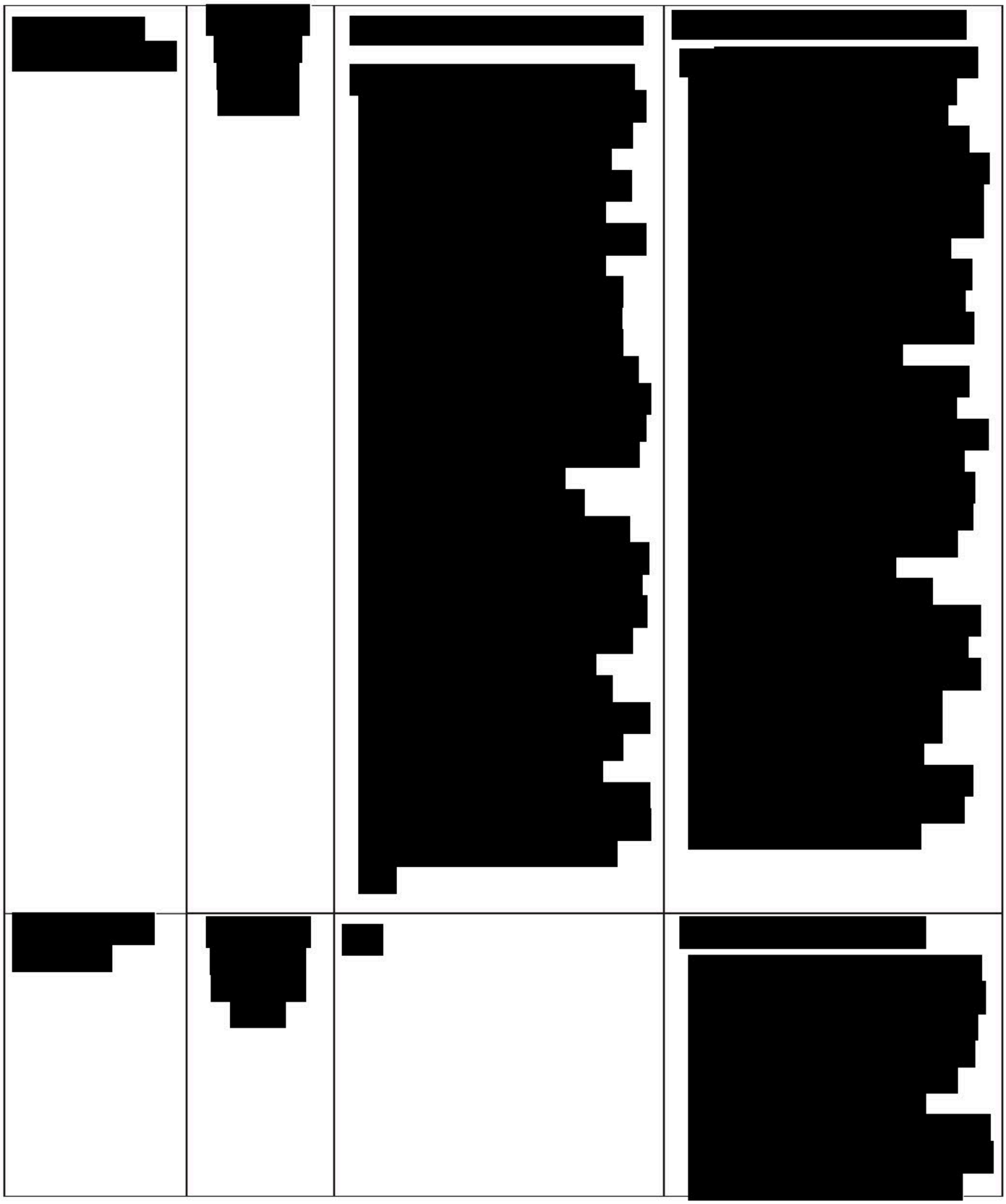

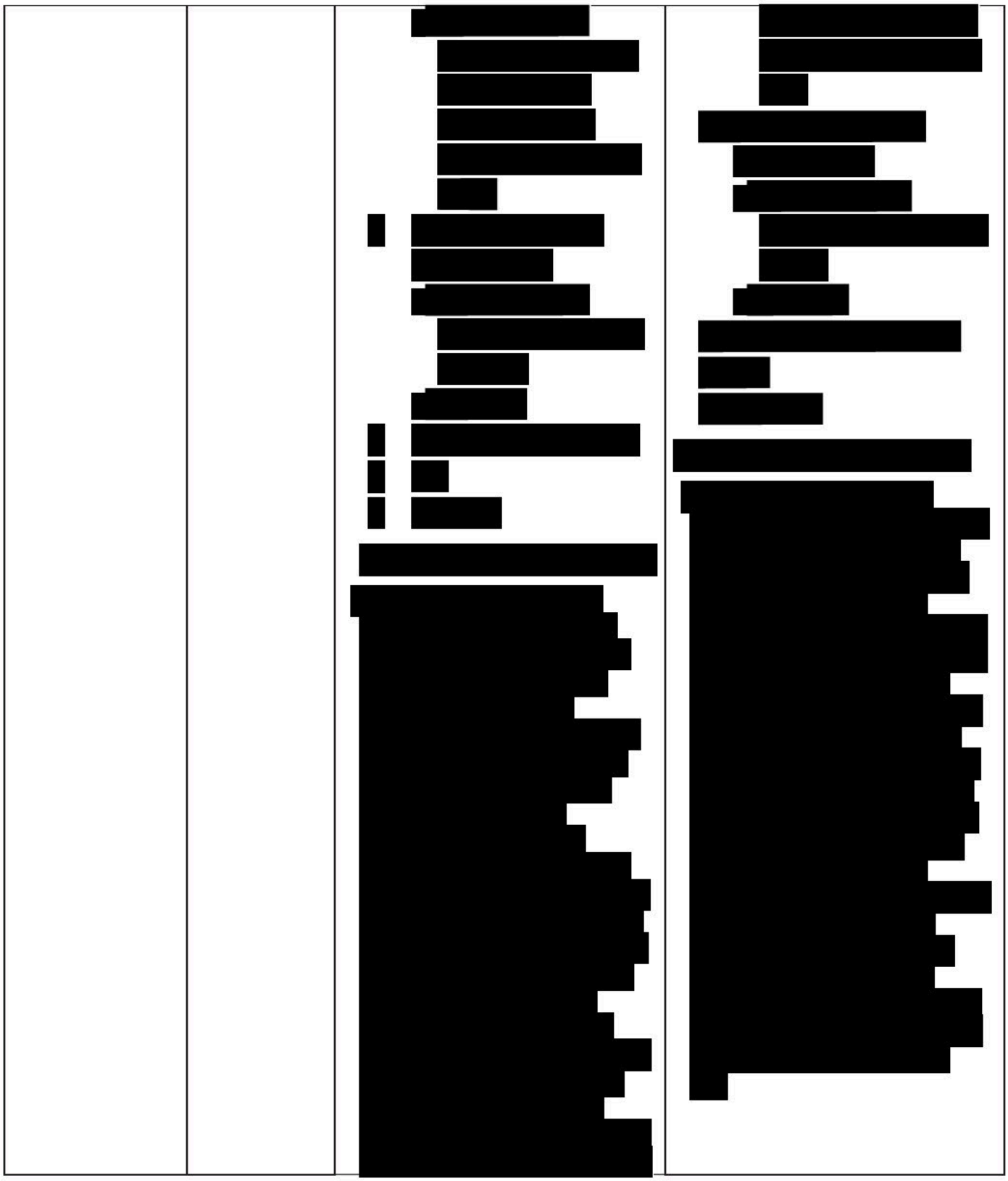

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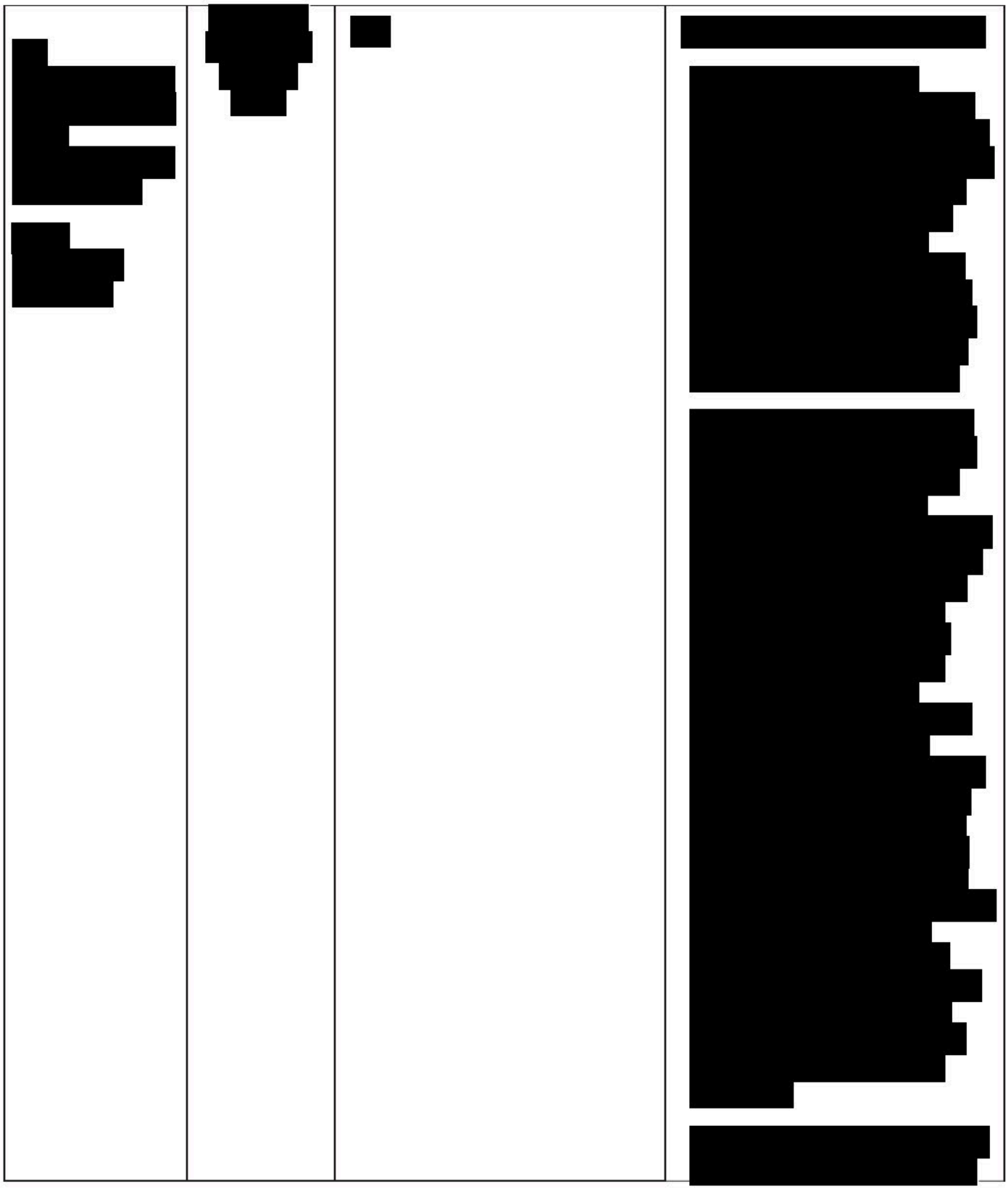

			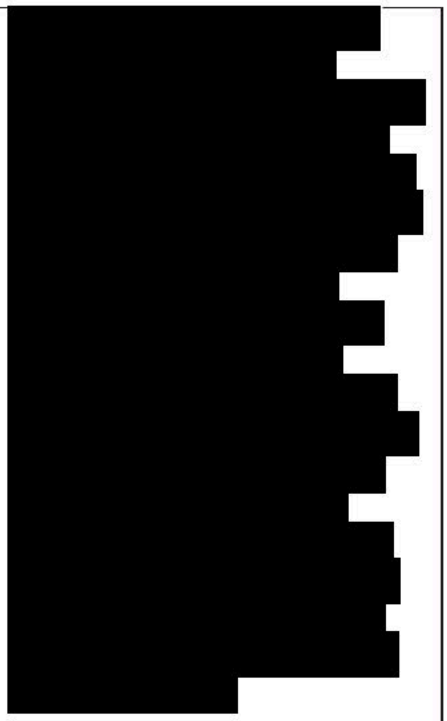

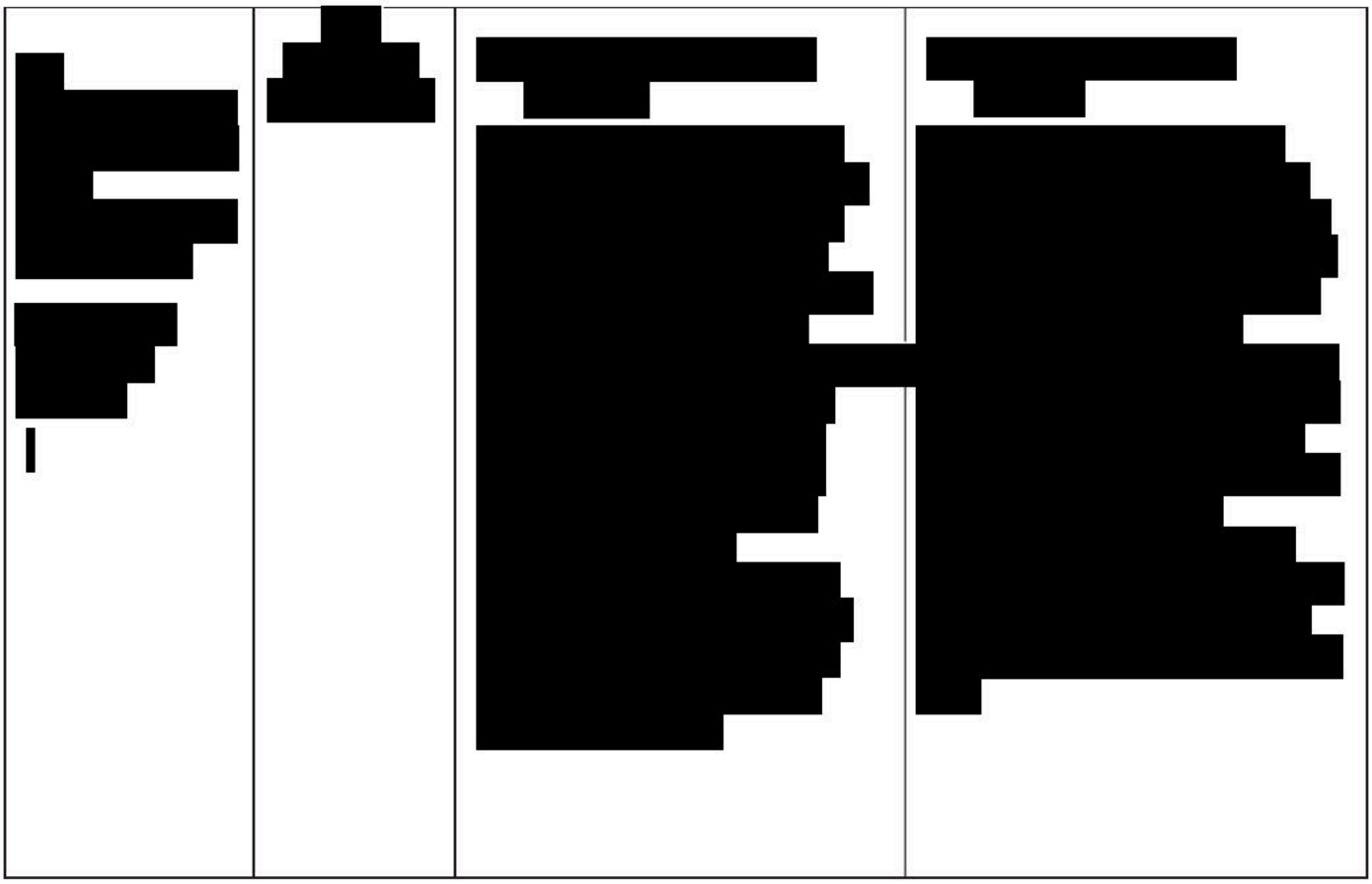

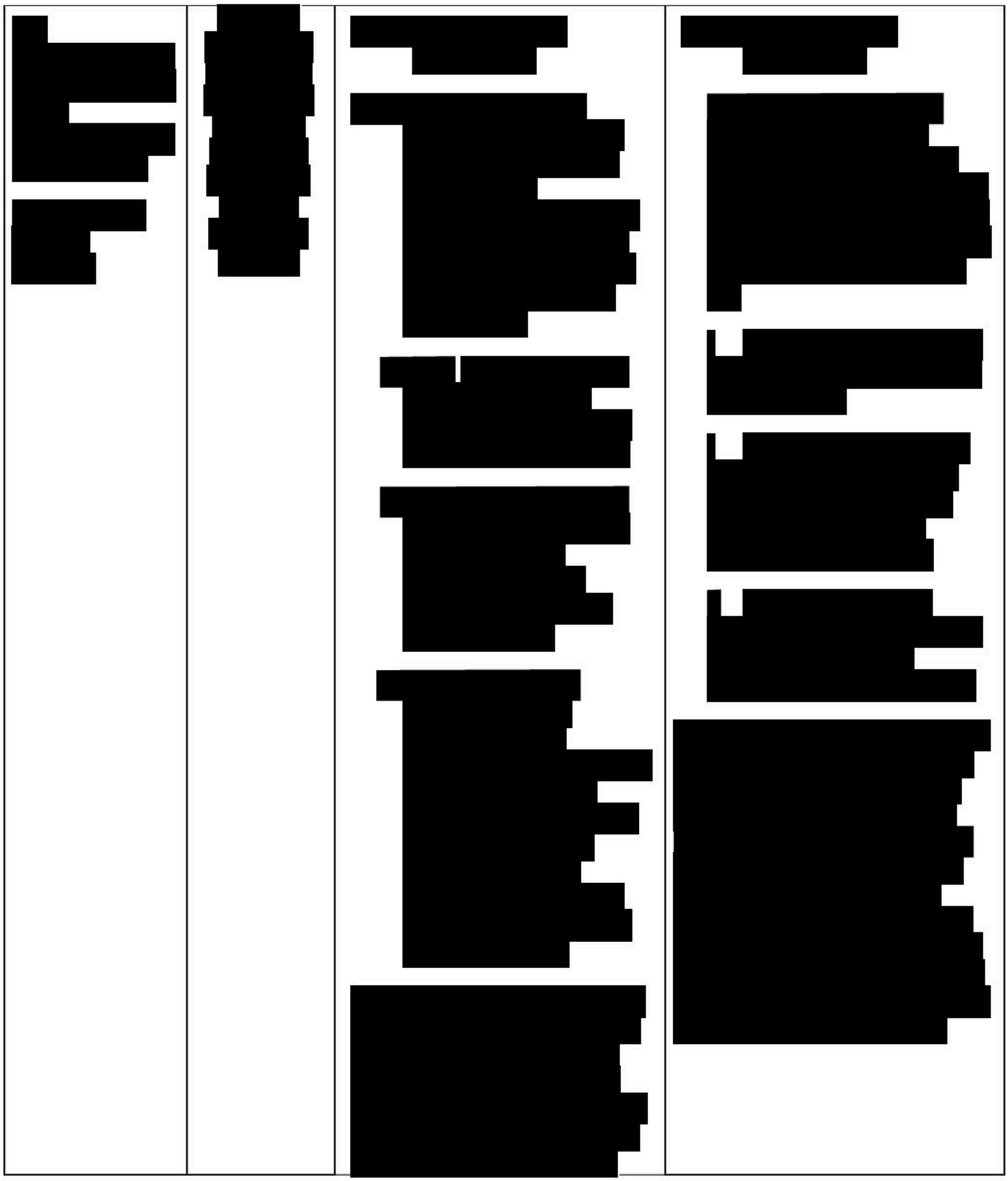

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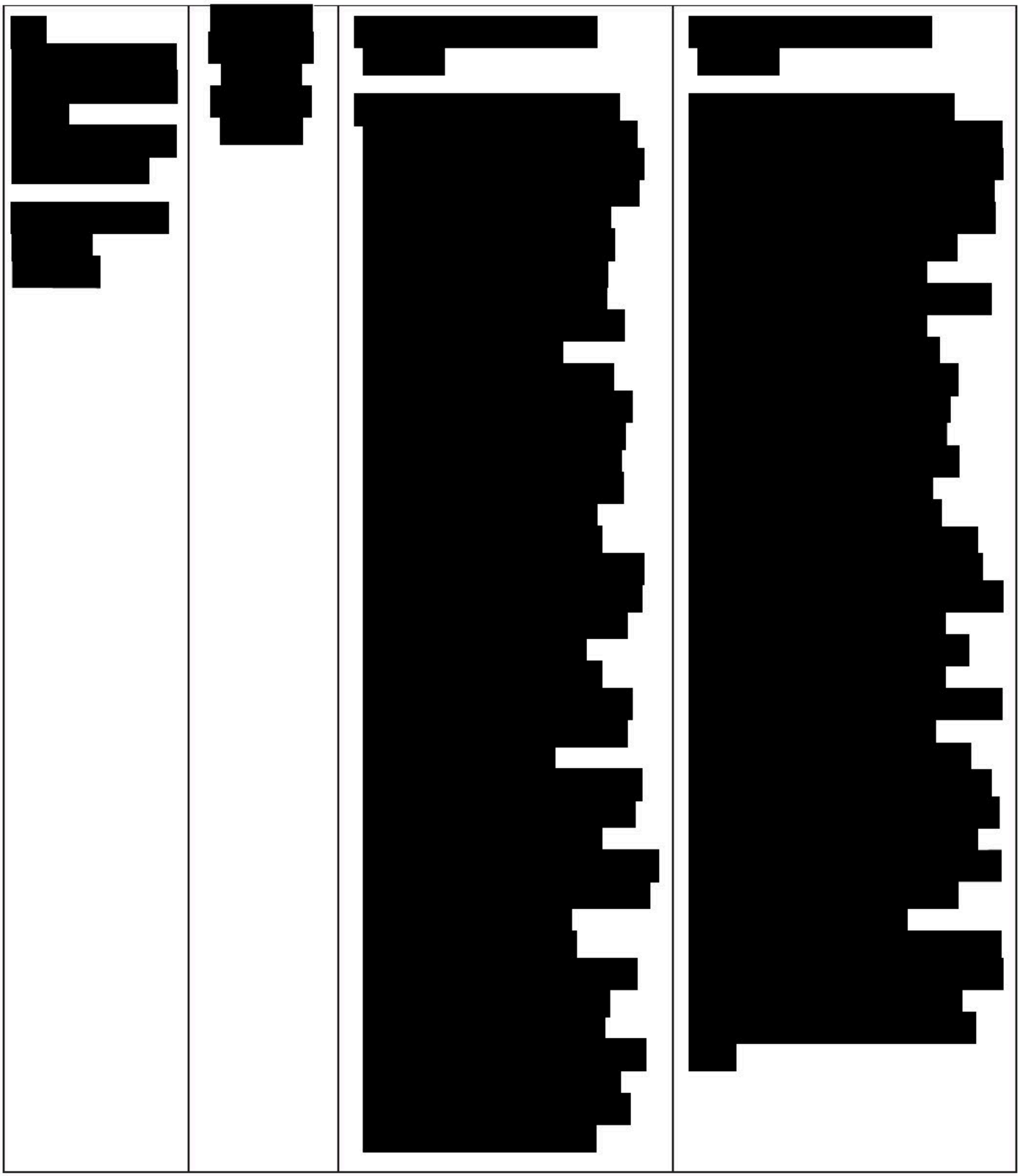

Appendix 5: Sponsor and Ora Approvals

Protocol Title:	A Single-Center, Double-Masked Evaluation of the Efficacy and Safety of PRX-100 in the Treatment of Early to Moderate Presbyopia
Protocol Number:	PRX100.FDAIIb
Final Date:	03Jul2018

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed 

Signed

Appendix 6: Investigator's Signature

Protocol Title:	A Single-Center, Double-Masked Evaluation of the Efficacy and Safety of PRX-100 in the Treatment of Early to Moderate Presbyopia
Protocol Number:	PRX100.FDAIIb
Final Date:	03Jul2018

I agree to implement and conduct the study diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the sponsor in confidence and, when this information is submitted to an institutional review board (IRB), ethical review committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed: [redacted]