WHAT SHOULD WE DO WITH THE INCIDENTALOME: INCIDENTAL FINDINGS IDENTIFIED IN THE COURSE OF GENOMIC ANALYSES?

Wendy Chung, MD PhD
Associate Professor of Pediatrics and Medicine
Whole Exome Sequencing

• Sequencing of the exome (all coding exons of all genes)
  – ~1-2% of the genome (30Mb)
  – ~20,000 genes
  – 180,000 exons

• Capture of the exons using array-based or liquid-phase hybridization (using DNA or RNA biotinylated “bait”).

• Sequence using NextGen technology

• Generates a massive amount of data which needs to be filtered to find “smoking guns”
Data Analysis Now

• Analysis pipeline required to “see” the results – BioInformatics Solution
  – Aligns patient sequence to the reference sequence
  – Calls the variants (SNV calling)
Data Filtering

• 10s of thousands of SNVs will be called
• We can’t look at and evaluate all of them
• Need to filter them so we see the important ones
  – By population frequency
    • At high % in 1000Genomes.org, pre-filter out
  – By presence of gene and/or mutation in HGMD or other database, often mistakes within databases
Have a seat Kermit. What I'm about to tell you might come as big shock...
Infantile Myofibromatosis

- 35 year old woman
- Had a history of multiple benign tumors in the head and neck, back and abdominal wall
- Pathologically called neurofibromas, leiomas
- No family history of these tumors. Breast and ovarian cancer in her maternal grandmother
- Tested for NF1, Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC). Negative results. Advised her mother to get BRCA1/2 testing.
As we are analyzing the sequence data

- Identify a BRCA2 mutation
- What do we do with this incidental finding?
"Incidental" or Secondary Results

• Variants that are not related to the patient’s indication for testing are called "incidental findings" or "secondary findings"

• What can this tell you?
  – Predisposition to an adult-onset condition
    • May provide information about risks for cancer, heart disease, Parkinson disease, etc.
  – Carrier status of a recessive condition
    • May have reproductive implications
  – Variants associated with drug response
    (Pharmacogenomics)
Return of Secondary Genetic Research Results

WES group

- Baseline questionnaire and vignettes
- Initial counseling session
- Pre-disclosure appointment questions
- Disclosure session
- 1 week post-disclosure phone interview
- 1 month f/u questionnaire
- 1 year f/u questionnaire

Comparison group

- Baseline questionnaire and vignettes
- 1 month f/u questionnaire
- 1 year f/u questionnaire
Genetic vignettes: Preference for Results

<table>
<thead>
<tr>
<th>Vignette</th>
<th>WES Group (n = 63)</th>
<th>Comparison Group (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier</td>
<td>94% 96%</td>
<td>85% 83%</td>
</tr>
<tr>
<td>Pharmacogenetic</td>
<td>97% 98%</td>
<td>87% 79%</td>
</tr>
<tr>
<td>Hered hemochromatosis</td>
<td>97% 96%</td>
<td>87% 79%</td>
</tr>
<tr>
<td>BRCA</td>
<td>97% 96%</td>
<td>88% 79%</td>
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<td>Pancreatic cancer</td>
<td>94% 88%</td>
<td>83% 79%</td>
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<td>Arrhythmia</td>
<td>95% 94%</td>
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<td>Cardiomyopathy</td>
<td>94% 94%</td>
<td>79% 79%</td>
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<td>Depression (hypothetical)</td>
<td>95% 96%</td>
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<td>Huntington</td>
<td>95% 96%</td>
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<td>Alzheimer's</td>
<td>95% 96%</td>
<td>87% 79%</td>
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<tr>
<td>Ancestry</td>
<td>95% 96%</td>
<td>100%</td>
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</table>
Carrier screening – over 80 different conditions identified in our subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tangier</td>
<td>ABCA1</td>
</tr>
<tr>
<td>Stargardt disease</td>
<td>ABCA4</td>
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<tr>
<td>Dubin-Johnson syndrome</td>
<td>ABCC2</td>
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<td>Pseudoxanthoma elasticum</td>
<td>ABCG6</td>
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<td>Hypoglycaemia, persistent hyperinsulinaemic</td>
<td>ABCC8</td>
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<td>Adrenoleukodystrophy</td>
<td>ABCD1</td>
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<td>Sitosterolaemia</td>
<td>ABCG8</td>
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<td>ASL</td>
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<td>ASS1</td>
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<td>BBS1</td>
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<tr>
<td>Bardet-Biedl</td>
<td>BBS4</td>
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<td>Maple Syrup Urine Disease</td>
<td>BCKDHA</td>
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<td>Maple Syrup Urine Disease</td>
<td>BCKDHB</td>
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<td>Biotinidase deficiency, partial</td>
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<td>Trichothiodystrophy, nonphotosensitive</td>
<td>C7orf11</td>
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<td>CDH23</td>
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<td>CEP290</td>
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<td>CFTR</td>
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<td>Cystic Fibrosis</td>
<td>CFTR</td>
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<td>CYBA</td>
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<td>G6PD</td>
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<td>GBA</td>
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<td>Deafness</td>
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<td>MCEE</td>
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<td>Meitterranean fever, familial</td>
<td>MEFV</td>
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<td>Myeloperoxidase deficiency</td>
<td>MPO</td>
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<td>methylmalonic aciduria</td>
<td>MUT</td>
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<td>NAGA</td>
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<td>CHIME:</td>
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<td>Polycystic kidney disease</td>
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<td>Progressive external ophthalmoplegia</td>
<td>POLG</td>
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<td>Muscular dystrophy, limb girdle</td>
<td>POMGNT1</td>
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<td>Antitrypsin alpha 1 deficiency</td>
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<td>Gitelman</td>
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<td>Cohen syndrome</td>
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<td>Von Willebrand Disease</td>
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## Medically Actionable Results Identified

<table>
<thead>
<tr>
<th>ID</th>
<th>Elected to receive</th>
<th>Disease Name</th>
<th>Gene</th>
<th>Mode of Inheritance</th>
<th>Elected to Receive</th>
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<tr>
<td>005</td>
<td>ALL results</td>
<td>Cardiomyopathy</td>
<td>MYBPC3</td>
<td>AD</td>
<td>Yes</td>
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<td>039</td>
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<td>MYH7</td>
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<td>117</td>
<td>ALL results</td>
<td>Brugada syndrome</td>
<td>SCN5A</td>
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<td>271</td>
<td>Limited results</td>
<td>HNPCC</td>
<td>MSH6</td>
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<td>279</td>
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<td>Hemochromatosis</td>
<td>HFE</td>
<td>AR (homozygous)</td>
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<td>200</td>
<td>ALL results</td>
<td>Factor XI deficiency</td>
<td>F11</td>
<td>AR (homozygous)</td>
<td>Yes</td>
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<td>270</td>
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<td>Familial Mediterranean fever</td>
<td>MEFV</td>
<td>AR (homozygous)</td>
<td>Yes</td>
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<td>Venous thromboembolic disease</td>
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<td>Yes</td>
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<td>276</td>
<td>ALL results</td>
<td>Glaucoma, primary open angle</td>
<td>WDR36</td>
<td>AD</td>
<td>Yes</td>
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<td>275</td>
<td>ALL results</td>
<td>Corneal dystrophy, Fuchs late-onset</td>
<td>ZEB1</td>
<td>AD</td>
<td>Yes</td>
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<tr>
<td>277</td>
<td>ALL results</td>
<td>Pituitary hormone deficiency</td>
<td>LHX4</td>
<td>AD</td>
<td>Yes</td>
</tr>
</tbody>
</table>

We identified actionable incidental results in 16.7% of individuals. We identified results in the ACMG 57 genes in 7.4% of individuals. This is not a trivial issue.
Actions following results disclosure

Cardiac
- RoR005 (cardiomyopathy): had follow up echocardiogram and shared results with adult sons who also had cardiac evaluations.
- RoR039 (cardiomyopathy): unknown if she has had a cardiac evaluation since disclosure of results
- RoR117 (Brugada): called for further information about cardiology referral, unknown if he had an evaluation

Cancer
- RoR271 (HNPCC): has had follow up visits with her GYN and GI to discuss screening, shared results with her cousin

Other
- RoR277 (pituitary hormone deficiency): had an appointment with an endocrinologist
Participant Outcomes

• Vast majority understood the process and were satisfied with their decision

• One patient with a history of psychiatric illness had significant anxiety immediately after results disclosure and did not recall any of her results or her reaction one year later

• One patient who was found to have the HNPCC variant called for a follow up discussion regarding screening and expressed that she was feeling anxious but empowered by her results.

“I knew it. My big fear was that I was going to be like my mother. I always say I don’t want to die like my mother did” ROR270, relating that she always knew that she would have what her mother had but now she has the knowledge to get the necessary screening to diagnose and treat cancer early
Survey and Interviews of Researchers

- Survey of the practices and attitudes of 234 members of the US genetic research community in August-October, 2012
  - NIH RePORTER
  - 2011 ASHG program
  - 34.7% response rate

- Performed qualitative semi-structured interviews with 28 genomic researchers
  - 56% response rate

Importance of Each Reason for Returning Incidental Results

- Would encourage participation in research
- Participants have a right to the info
- It could be life saving; there's a moral obligation to return life-saving
- Other disciplines return incidental findings
- Concerned over legal ramifications over adverse outcome

Genet Med. 2013 Jun 27. doi: 10.1038/gim.2013.87
Reasons to Return IFs: Sample Quotes

- Morally uncomfortable not to return results
  - To withhold such medically actionable information is morally uncomfortable.
- Researcher responsibility
  - “Look, these are my patients. I’m going to tell them.” (R-I 5)
- Subject autonomy/rights:
  - “A person owns their own genome. If they want to know what their genome is... they have a right to know, period. The implications of the knowledge don’t matter.” (R-I 22)
- Beneficence:
  - “I think that returning of incidental results is often appreciated by research subjects as a way of demonstrating that the researchers care about the benefit to them and not just the benefit to the research”. (R-S 001)

Importance of Each Reason for **Not** Returning Incidental Results

- Insufficient staff
- Cannot afford CLIA confirmation
- Lack of expertise to interpret and return results
- Most results are of uncertain implication for clinical care
- Burden and distraction from primary research
- IRB does not allow it
- Participants would expect medical care from research
- I do not know if my participants want this information
- Participants can get this information from their healthcare providers

*Genet Med. 2013 Jun 27; doi: 10.1038/gim.2013.87*
Reasons **Not** to Return IFs: Sample Quotes

• Liability concerns:
  – Seems [it] could open up liability even if we did nothing because it could be argued we should have done something. So there is safety in not being allowed to do anything.” (R-S 118)

• Subjects won’t understand:
  – Subjects will inevitably be incapable of distinguishing the various shades of gray relating to potential false positive and false negative findings. (R-S 077)

• Uncertain results could be harmful
  – If we don’t know what something means, we’re doing more of a disservice than a service by telling patients...Our credo is ‘do no harm.’ Sometimes telling people something that you don’t understand does harm. (R-I 17)
Reasons **Not** to Return IFs

- **Lack of resources:**
  - We just don’t have the money to go back and re-test this, to re-analyze these sequences, to see if people have these variants... It comes down to cost.”

- **Diverts limited resources from doing research:**
  - The number of potential IFs is essentially infinite. The amount of overhead for identifying and reporting incidental clinical findings would destroy the research enterprise in genetics.” (R-I 28)

- **Hampers long-term social benefit of research:**
  - “If we cut back deeply on the research, we won't get to that point in the future where everybody's genome will be sequenced, and become part of standard clinical care, rather than a research project.” (R-I 18)

- **Can pose significant danger to the field:**
  - Several expressed vociferous opposition to returning IFs. “I feel very strongly that the field is heading over the cliff on this issue...IFs should not be returned to subjects – full stop.” (R-S 077)
Other themes

• Unsure/mixed views
• Questions of what to return
• Who should return IFs?
• Who should decide whether IFs are returned?
• Perceptions of genomic research participants’ views
Themes Concerning How Researchers Make Decisions Concerning Return of IFs

• Assessing multiple factors jointly
  – Providing uncertain results and explaining the uncertainty
  – Making *judgment calls*
    • Interpretations may vary over time
• Who should decide
  – Leave it up to the participant
    • But they may decide without fully understanding the complexities
• Leave it to the PI’s discretion
  – Override patient preferences?
  – Offer possibility, not promise of return
  – Err on side of giving results vs. err on “conservative” side
  – Maintain “willful ignorance”
• Seek external expertise
  – Within study team
  – External to study team

PI: Principal Investigator
Themes Concerning How Researchers Make Decisions Concerning Return of IFs

- Contextual factors/roles of institutions and other governing bodies
  - Biobanks
    - Biobank has pre-established parameters or not
- IRBs
  - Experienced with issue or not
  - In agreement with researcher or not
  - Can provide a rationale to not return results ("The IRB said no")
- Governmental policies
  - In the US, many labs are not CLIA-approved and CLIA confirmation is costly.
  - Policies differ in other countries:
    - In the developed world
    - In the developing world

CLIA: Clinical Laboratory Improvement Amendments
Genet Med. 2013 Jun 27. doi: 10.1038/gim.2013.87
Reasonable Amount of Time for Informed Consent for Return of Incidental Findings

Genetics in Medicine: Accepted August 2013.
The Dilemma

- Standard approaches for obtaining informed consent are not likely to be effective at conveying all the information identified by our respondents as worth communicating—in the time available to do it.
What’s the Solution?

• Assuming that we maintain a commitment to participants making informed choices about receipt of IFs, innovative solutions are needed

• Based on survey responses, interviews, and literature review, we identified 4 leading models to consider
  – 1st model reflects traditional approach to consent, while the other 3 embody creative alternatives
  – Recognize that there are likely to be multiple permutations, including hybrid approaches that blur the boundaries between them, and other models may develop
Traditional Consent:
Incorporate discussion of the issue into consent to participation in the underlying research

Potential Advantages
- Resembles traditional process, familiar to the research community
- Participant receives all IF information prior to deciding whether to participate
- Participant maintains choice about types of IFs to receive, or about opting out

Potential Disadvantages
- Adds time and information to lengthy and complex process
- Participant preferences may change after initial consent
Staged Consent

Staged Consent:
Brief mention of incidental findings at the time of initial consent; more detailed consent when/if reportable results found

Potential Advantages
- Reduces time spent discussing IFs during initial consent; more detailed information provided later if IFs occur
- Participant makes decisions on IFs closer to the time of receipt, can consider current circumstances
- More detailed and specific information for participant
- Participant maintains choice about types of IFs to receive, or about opting out altogether

Potential Disadvantages
- Following-up and recontacting participants costly and burdensome
- Participant’s decision to enroll made without full information about potential return of IFs
- Recontacting participant may reveal unwanted information about an IF, with negative impact on participant
Mandatory Return

**Potential Advantages**
- Simplifies consent at enrollment: participant receives information only on selected IFs, does not have to choose which findings to receive
- Researchers’ obligations to return IFs clearly defined and limited to a pre-determined list
- Degree of choice maintained about whether to participate in the study

**Potential Disadvantages**
- Participant choice restricted—can’t choose which findings to receive, and cannot refuse to accept designated findings
- Lack of participant choice may be disincentive to enroll in genomic research
- Efforts to follow-up and recontact participants could be costly and burdensome for researchers

Mandatory Return: Obtain consent to return of specific categories of IFs at the time of—and as a condition of—enrollment
Outsourced Model

Outsourcing:
Refer participants to third parties for consent and return of incidental findings

Potential Advantages
• Researchers don’t have to spend time explaining implications of IFs
• Costs associated with return of IFs avoided, including recontacting participants, hiring additional staff, etc.
• Participant spared immediate task of deciding which secondary findings to receive
• Researchers’ obligations simplified: return each participant’s raw data

Potential Disadvantages
• Though participant receives all genomic data, may not become aware of medically significant data
• Services for genomic interpretation and counseling not widely available at present
• May exacerbate health disparities, since further interpretive services may be costly and limited to wealthy participants
Which Model is “Right?”

- No perfect model—approach selected will depend on assessment of researchers’ obligations and practicality
- Assessment depends in part on empirical data not yet available, e.g., which model leads to best informed decisions or reduces adverse consequences
- Balance likely to change over time, e.g., as identification of variants as pathogenic or not improves and becomes increasingly automated
Retrospective versus Prospective Research

• Same set of rules for samples collected previously?
• Consents did not envision this possibility
• Often NO results are returned, primary or secondary
• Samples were collected up to 25 years ago and many participants are deceased, lost to follow up or are now adults when they were previously children at time of enrollment
• Prospective enrollment affords different opportunities to discuss options and maintain contact with participants (email/portals)
What to Return?

• Small number of bins

• Clinically actionable results of high penetrance (cancer genes)
  – For colorectal and breast cancer the ‘treatment’ is increased screening. If these folks don’t have insurance, that becomes a problem.” (R-I 5)
  Some researchers considered interventions such as those to reduce breast cancer risk problematic. “The prophylactic treatments are not so wonderful that I feel compelled to call. But again this is very subjective.” (R-I 4)

• High penetrance but only personally actionable (Huntington Disease)
  – “You can argue that you could benefit – you’d live your life differently, write your power of attorney differently.” (R-I 6)
American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

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ACMG Guidelines for CLINICAL exome sequencing

• 56 genes
  – Cancer: BRCA1/2, Lynch syndrome, Li-Fraumeni syndrome, FAP, VHL, MEN, PTEN, RP, TSC, NF2
  – Cardiac: LQT, CPVT, Cardiomyopathy, ARVC, Marfan/aortic dissection, familial hypercholesterolemia
  – Malignant hyperthermia

• Mandatory reporting to clinician

• Regardless of age of patient, including children

• Regardless of indication and includes tumor/normal comparison
Concerns with the guidelines: 56 genes

- Lack of robust, well curated mutation databases
- Positive rates of 3-15%
- Penetrance similar with population ascertainment as clinical ascertainment ???
Concerns with the guidelines: mandatory disclosure

- Some patients find genetics stigmatizing
  - Orthodox Jewish
- Some patients have already opted out for specific tests on this panel, why force them now?
- Specific indication of tumor sequencing did not include input from oncologists
- ACMG policy revised in April, 2014 to remove mandatory disclosure
Concerns with the guidelines: mandatory disclosure to children

• Contradicts AAP and ACMG guidelines not to perform predictive testing in children when there is no intervention until adulthood
• Long term effects on psychosocial development of the child and vulnerability
Facilitators to Implementation of Return of Secondary Findings

- Educational/consenting materials
- Public and provider education
- Well curated mutation databases
- Data on penetrance from population ascertainment
- Analysis pipelines to limit effort to identify secondary findings robustly/accurately
Summary

• Whole genome sequencing will be increasingly used in research and clinical practice
• Issues in research and clinical practice have similarities but are distinctly different, and research of clinical practice is increasingly blurs that boundary
• Must develop policies for return of secondary findings for research and clinical care
• Policies should be based upon empirical data and should await implementation until infrastructure available to support good medicine
• Research question may be a short lived problem as more patients have clinical sequencing
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